GASTRECTOMY AND THE BLIND-LOOP SYNDROME

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THERE are patients whose health has been ruined by intestinal malabsorption following gastrectomy for peptic ulcer. Physicians and surgeons have pondered this problem for many years, but it is our belief that they have placed the emphasis on the wrong part of the complex pattern of causes. Consequently, methods aimed at prevention have been inept, and the toll of unnecessary tragedies continues.

Hurst (1913, 1929) was the first to describe the diarrhœa, and other symptoms later called " dumping ". He stated that a large stoma permits precipitate emptying, and thus causes symptoms. This became the accepted view. But the surgeons said that a generous stoma was one of the requisites for the success of a gastroenterostomy. Thus, Eusterman and Balfour (1936) advised that the stoma should include the whole width of the posterior wall of the stomach, from the lesser curvature, downwards and to the left, to the greater curvature at its most dependent point. These authors stressed, as also did Moynihan (1926), that failure is often due to inadequate drainage through a stoma which is too small or too high.

We thus find the large stoma stigmatised as a cause of failure, yet advocated as a condition of success.

Further, Eusterman and Balfour wrote that " too rapid emptying of the stomach . . . may cause a train of disturbances ", but, " from the roentgenographic standpoint, all resected stomachs appear to empty rapidly, yet few of the patients complain of any discomfort ". Later, Custer, Butt, and Waugh (1946), also from the Mayo Clinic, expressed themselves as similarly puzzled by the fact that all patients show rapid emptying into the efferent loop, but only a few experience dumping.

Moynihan (1926) also described this " too rapid emptying of the stomach " and the diarrhœa, which " may be slight, or may be so serious, so constant, uncontrollable and exhausting as to be the immediate cause of death ". He concluded that " no adequate explanation of the complication can be given ".

Today, the question is still confused. The main emphasis is still placed upon too-rapid emptying, or loss of " hopper function " of the stomach. The food is said to pass down the intestine in advance of the bile and pancreatic juice, thus establishing a " pancreatic-cibal asynchrony " (Royal Society of Medicine 1959, Herrington et al. 1959).

Influenced by this hypothesis, surgeons had retained more, or even all, of the stomach, adding vagotomy; some have anastomosed the afferent loop to the greater curvature of the stomach, even adding a deliberate obstruction of the efferent loop at the lesser curvature.

Hypotheses can be salutary, but only if they are valid. And they are valid only if they can explain the facts.

We therefore present a summary of the facts, firstly, those already well known; secondly, brief case-records of patients recently seen in our own practice.

The Facts

Fluoroscopy shows that normally the duodenum and first loop of jejunum empty so rapidly that the movement can scarcely be followed by the eye. The movement becomes slower as it passes downwards, so that the ileum retains its contents for some hours. The " asynchrony " between the discharge of biliary-pancreatic secretions into the duodenum and the discharge of food through the gastrojejunal stoma is normally a few seconds or less, and is so short that it cannot prevent adequate mixing. In practice, however, the " asynchrony " can be increased by obstruction in the afferent loop, and then becomes a serious factor. But even then the " asynchrony " and " loss of hopper function " are not the primary and essential factors, for it is the obstruction which is the basic cause.

Dumping and diarrhœa were first described as results of gastroenterostomy, not of gastrectomy.

Results of gastroenterostomy are not better, but worse, with a small or high stoma.

After vagotomy, the paradox may arise of delayed emptying of the upper part of the alimentary tract, together with diarrhœa.

Conservative operations—antrectomy or gastroenterostomy, with vagotomy—are still followed by " the dumping syndrome " and severe weight loss (Everson et al. 1947).

In four patients out of five, conversion of a Billroth-II to a Billroth-I gastrectomy will cure severe dumping symptoms.

In a fifth patient, this conversion may fail.

Dumping symptoms and diarrhœa after a Billroth-II operation may be cured by lifting up and supporting the afferent loop (Mimpress and Birt 1948, Capper and Butler 1951), or by Braun anastomosis between afferent and efferent loops (Schofield and Anderson 1953), or by the " pantaloon " anastomosis of Steinberg (1955).

Dumping symptoms and diarrhœa may follow total gastrectomy, but we have observed patients five, seven, and ten years after total gastrectomy with no gastrointestinal symptoms.

In a series of patients after the Billroth-II operation, all may show rapid emptying into the efferent loop, but only a few of these may experience symptoms.

Precipitate emptying of gastric contents into the afferent loop may be associated with dumping symptoms, but patients with dumping symptoms may show no emptying into the afferent loop (Goligher and Riley 1952).

After the Billroth-I operation, dumping symptoms and diarrhœa are less frequent and severe than after the Billroth-II.

Historically, the great masters who fashioned the details of the Billroth-II methods (Mikulicz, Eiselsberg, Krönlein, Reichel, Pólya, Hofmeister, and Finsterer) pointed to the importance of placing the afferent loop to the lesser curvature, because the reverse placement encouraged retrograde filling and this was to be avoided. In their careful and prolonged follow-up of thousands of patients, the dumping syndrome was not a major problem.

More recently, a few surgeons have placed the afferent loop to the greater curvature (*anastomose inversée*), and

have even contrived a minor obstruction of the efferent loop at the lesser curvature. In Australia, gastrectomy by this technique has not been successful, and vagotomy, with drainage operations, has been preferred. American clinics have not presented a late follow-up after *anastomose inversée*. A few brief references in the recent literature have mentioned the method only to condemn it (Müller 1956, Kötö 1958).

Some Case-records

Case 1.—Aged 47. In 1954, had a Billroth-II operation for duodenal ulcer. This was followed by vomiting and diarrhœa. In 1958, a hernia of small intestine through the mesocolon was repaired; followed in three weeks by separation of adhesion, and cholecystectomy for gallstones. Vomiting began, diarrhœa and weight-loss became more severe, and the patient was transferred from the country to St. Vincent's Hospital on April 15, 1959, suffering from severe malnutrition and steatorrhœa. He also had advanced rheumatoid arthritis. Barium meal showed gross delay in the emptying of his gastric remnant, and of the upper jejunal coils (fig. 1). Under medical treatment, his vomiting ceased, and his condition improved. But eight weeks after admission to hospital, he passed blood in the urine and was found to have a carcinoma of the bladder from which he succumbed.

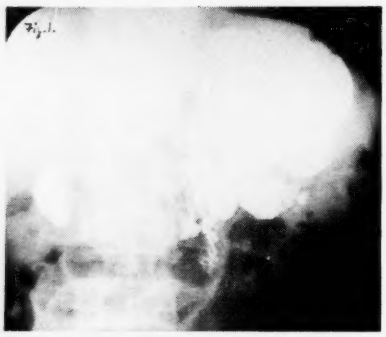

Fig. 1—Case 1. Delay in emptying of gastric remnant and upper jejunal coils.

Case 2.—Aged 43. In 1958 had a Billroth-II operation, performed elsewhere, for gastric ulcer. Soon after she began to vomit, lose weight and suffer from diarrhœa, and she was seen in consultation by one of us (W. B. H.). She had wasting and widespread œdema, ascites, steatorrhœa, and severe hypoproteinæmia. Barium meal showed a large dilated afferent jejunal loop which still contained barium seventeen hours after the meal (fig. 2). Fluoroscopy showed that the stomach emptied into the afferent loop, and this emptied back into the stomach, so that a pendulum movement resulted. At laparotomy, performed elsewhere on Sept. 1, 1959, a thickened, writhing, dilated afferent loop was seen, and dark foul-smelling fluid poured from this when the stoma was opened in an attempt at reconstruction. Gastric and colonic fistulæ resulted, and, in spite of two further laparotomies, the patient died on Oct. 18, 1959.

Fig. 2—Case 2. Barium retained in dilated afferent jejunal loop, seventeen hours after meal.

Case 3.—Aged 50. Had partial gastrectomy for duodenal ulcer in January, 1957; reoperation for gastrocolic fistula in August, 1958; vagotomy in December, 1958, for an ulcer in the efferent jejunal loop. At the last operation, the pancreas was reported to be normal. In 1959, she was seen by us, and was admitted. She had diarrhœa, severe malnutrition, weight loss (from 10 st. 4 lb. to 6 st. 4 lb.), gross œdema of the lower limbs, and dry thin scaly skin with large ecchymoses. Investigations revealed gross steatorrhœa and hypoproteinæmia. Perhaps this, as well as altered pH in the intestine, contributed to the diarrhœa. Radiographs showed consistent filling and dilatation of the afferent jejunal loop (fig. 3). Her response to intensive therapy was only partial and temporary, and she died on Dec. 11, 1959. Necropsy findings included a stomal ulcer, a grossly dilated afferent jejunal loop, enteritis, and several non-beta-cell pancreatic microadenomata. (Among patients with these tumours, a few suffer from diarrhœa, and most of them have had a constriction of the duodenum in its distal parts, or the jejunum, either by the pancreatic tumour or by a jejunal ulcer.)

Fig. 3—Case 3. Dilatation of afferent jejunal loop.

Case 4.—Aged 50, had had gastroenterostomy in 1947, for gastric ulcer, followed one week later by reoperation for vomiting. On account of repeated hæmorrhages, partial gastrectomy was performed elsewhere, in 1951. About six weeks later, diarrhœa began and continued, with 6 to 25 bowel actions daily. Her appetite remained excellent, but, in spite of frequent big meals, her weight fell from 7 st. 2 lb. to 6 st. 5 lb., and investigations revealed gross steatorrhœa. Barium meal in 1959 showed barium passing back into the afferent loop, but stopping abruptly, as though obstructed, an inch or two proximal to the stoma (fig. 4). At about this time, the patient bled per vaginam. A carcinoma of the cervix was discovered for which she is still under treatment.

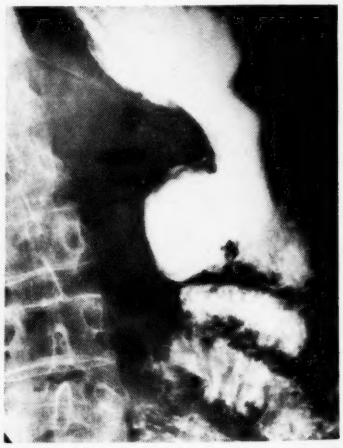

Fig. 4—Case 4. Stasis in afferent jejunal loop.

Case 5.—Aged 50, had diarrhœa and weight-loss after Billroth-II gastrectomy. A barium meal showed a picture similar to fig. 4.

Case 6.—Aged 42. Had had a partial gastrectomy, with *anastomose inversée* five years previously for duodenal ulcer. She was reasonably well for two to three years. Then she began to get attacks of fullness after eating, with copious brown

vomiting, diarrhœa, and weight loss. Intermittent spontaneous improvement would occur. Barium meal showed a dilated afferent loop. She was referred for opinion by her physician, and we advised reoperation.

Case 7.—Aged 56. In 1952, had cholecystectomy for gallstones, later a choledochoduodenostomy and sphincterotomy. But the pains persisted. In 1957, she had a partial gastrectomy performed elsewhere for a small gastric ulcer. Her pains disappeared, but diarrhœa began—4 or 5 large yellow offensive motions a day—and she lost 28 lb. in two years. Investigation revealed gross steatorrhœa. Barium meal showed a gastrectomy of adequate extent, but barium passed back into the afferent loop and stopped abruptly about one inch from the stoma (fig. 5). A choledochogram showed an unusual accumulation of dye in the duodenum, with delayed emptying, and the duodenum appeared wider than in the pregastrectomy barium meal. On Feb. 2, 1960, at laparotomy, the liver was found adherent to afferent loop and stoma. It was felt that a freeing of this would be only temporarily effective, so a lateral anastomosis was made between the second part of the duodenum below the mesocolon and an upper jejunal loop. After operation the diarrhœa ceased, and the motions have remained normal, and she has gained over 14 lb. in the nine months since operation.

Fig. 5—Case 7. Stasis in afferent jejunal loop.

Explanation of the Facts

It is evident from these data that "dumping" symptoms and diarrhœa are not primarily and essentially caused by: (1) altered time-relationships with failure to mix; (2) large stoma; (3) loss of this or that fraction of stomach; (4) loss of hopper function; (5) loss of digestive secretions; or (6) precipitate emptying into the efferent loop. The symptoms can occur in the absence of any one of these factors—e.g. (a) even with the small stoma of an œsophagojejunostomy; (b) with the stomach still retaining its secretory functions after gastroenterostomy; (c) with the reservoir function still intact, and even exaggerated after vagotomy; and (d) with ample, and even exaggerated, opportunities for the mixing of food and pancreatic secretions, as in cases 1, 2, 3, and 6. Moreover, a patient may remain free from digestive symptoms even after total gastrectomy.

The only common factor in the above patients, and, therefore, the primary and essential one, is stasis in the duodenojejunal loop. In two of the patients (cases 2 and 7) fluid was removed from the afferent loop during operation, and culture revealed a mixed bacterial flora. These patients had previously improved under treatment with broad-spectrum antibiotics. Stasis in lower intestinal loops is already well known as a cause of malabsorption—the "blind-loop syndrome". If its importance is also recognised in the uppermost loop, the duodenojejunal, then an important piece falls into place in the puzzle of the postgastrectomy syndrome.

To achieve a permanently good result after Billroth-II gastrectomy, stasis in the afferent loop must be avoided. Symptoms may improve or disappear during the first twelve months after operation, because the congestion and rigidity in healing tissues, especially if subjected to low-grade infection, may take twelve months to disappear, as can easily be observed in the scar on the abdominal wall. Conversion of a Billroth-II operation to a Billroth-I, and anastomoses between afferent and efferent loops, and suspension operations on the afferent loop cure symptoms, because there has been some degree of afferent-loop obstruction. Sometimes the conversion to a Billroth-I operation fails, perhaps because of some degree of jejunal obstruction at the site of repair of a distorted and thickened jejunal loop. Other factors may also operate. Vagotomy causes stasis in the stomach and first part of the intestinal tract. A Billroth-I operation involves a considerable degree of vagotomy, and it diminishes secretion.

Stasis in the duodenojejunal loop may therefore be caused by (1) mechanical constriction, (2) a to-and-fro emptying between the afferent loop and the stomach, and (3) vagotomy.

Effects of Afferent-loop Obstruction

Obstruction of the afferent loop may provide several groups of symptoms:

1.—Epigastric pain or discomfort, worse after meals.

2.—Widespread autonomic reflex effects, and internal and external secretory disturbances of the liver and pancreas.

3.—Intermittent copious vomiting of bile.

These three groups have been well recognised but we would add a fourth. It is our opinion that malabsorption, with its diarrhœa, anæmia, and nutritional disturbances, must also be added to the symptoms caused by afferent-loop stasis. This has not been widely recognised. Indeed, Card disagrees on the grounds that this part of the gut is "extremely active and empties itself readily". But he pays an undeserved compliment to the surgeon in supposing that the ideal intestinal order always remains exactly the same after operation (Royal Society of Medicine 1959). The afferent loop is not a blind loop, unless the surgeon makes it so.

Radiological Diagnosis of Afferent-loop Stasis

After a properly constructed gastrectomy, the opaque meal should pass easily and freely into the efferent jejunal loop. The afferent loop should show, at most, a slight trickle of barium gradually tailing off before the second part of the duodenum is reached, just enough to show that there is neither obstruction at the critical point near the lesser curvature, nor any dilatation of the loop (fig. 6).

Patients suffering from afferent-loop stasis fall into three radiological groups:

1.—There may be no radiological signs, because the stasis is caused by obstruction at the point where the afferent loop meets the stomach, and barium is, therefore, prevented from outlining the obstructed loop.

2.—In some patients the obstruction is at a point slightly proximal to the stoma, and this is shown when the barium passes freely back into the afferent loop for one or two inches and then stops abruptly.

3.—In other patients, the stasis is caused by free retrograde emptying of the stomach into the afferent loop, and then emptying of the afferent loop into the stomach, so that a pendulum movement results.

Fig. 6—Ideal radiographic appearance after gastrectomy.

Fig. 7—The first principle in Billroth-II reconstruction—the quiet confluence of unobstructed streams.

Non-filling of the afferent loop may, therefore, be associated with a perfectly constructed anastomosis, or with a seriously obstructed loop. If the patient suffers from malabsorption, it is advisable to do a choledochogram in the hope that the duodenum may be seen on the radiograph.

Causes of Malabsorption

It is our view that emphasis should be shifted from precipitate gastric emptying to stasis in the afferent loop, as a cause of malabsorption after gastrectomy. Other causes which may contribute include pancreatitis, and perhaps defects in the intestinal mucosa.

First Surgical Principle of Prevention

A first principle of gastrointestinal surgery, which must be rigorously applied in gastric surgery, is that an end-to-side anastomosis must achieve a *quiet confluence of unobstructed streams*.

This means, among other things, that the anastomosis must be " en-Y ", whether between stomach and intestine, or between two loops of intestine. The old masters wrought well. There is no place for anastomosis " en-T ", still less for the emptying of one viscus at an acute angle against the stream of the other (the *anastomose inversée*). Such junctions effect a turbulence rather than a confluence. They are avoided by Nature, in the rivers, in plants, and in the animal body. They cause an increased mechanical stress, and an accelerated mechanical destruction. But over and above this, in the digestive tract they interfere with local functions by unduly prolonging the digestive phase in part of the bowel. Increased functional stress, disturbance of bacterial flora, and inflammation are the invariable accompaniment of stasis in a hollow viscus.

For years, one of us has made every effort to apply this principle in the surgical treatment of the afferent loop, and our series of gastrectomies for ulcer, numbering nearly four hundred, has not been complicated by diarrhœa and malabsorption. Figs 6 and 7 show the ideal to be aimed at.

Detailed Application of this Principle

The afferent loop must be placed to the lesser curvature.

It must not be too long. If slightly too long, it may kink. If grossly too long, it may also allow the passage behind it of another intestinal coil. It must not be too short, for obvious reasons.

At the uppermost point of the loop, where it turns downwards to meet the lesser curvature, there is a tendency to kinking which must be prevented by lifting the antimesenteric border away from the mesenteric border, by suspending it to the lesser curvature of the stomach above the stoma. This is done by means of the Kapeller suspension stitches. These must be so applied that torsion is not produced by, for example, fixing the apex of the jejunal loop in front of the lesser curvature. The stitch should take up the anterior surface of the stomach, just in front of the lesser curvature, then the posterior surface just behind it, then the posterior surface of the jejunum just behind its greatest convexity, and then its anterior surface just in front.

The incision in the stomach must pass downwards and to the left, so that the stoma and the efferent loop are continued in the one staight line down to and away from the greater curvature. If too much of the greater curvature is removed, obstruction is caused by Visick's " question-mark deformity ".

The incision in the jejunum must be placed accurately on the antimesenteric border, and not obliquely, otherwise torsion results.

The handling and suturing of the visceral walls must be refined and delicate, to avoid excessive " anastomositis " with its scarring and fixed mucosa. The niceties of suturing have been described earlier (Kinsella 1959).

In retrocolic anastomoses, the mesocolon must be so sutured that kinking of the jejunum is avoided.

In antecolic anastomoses, the omentum must be placed so as to prevent adhesion of the afferent and efferent loops to each other, or to the parietal incision.

Conclusion

It is our opinion that malabsorption following gastrectomy could be largely prevented, and some sufferers could be salvaged, by the application of the principles described in this paper. Gastrectomy is a precision operation. The solution of the problem of its complications lies in perfecting the technique of the operation as it is applied, not in the devising of new combination operations, which involve the same old dangers, and add new ones of their own. Vagotomy adds gastric retention, necessitating a considerable number of re-operations (even when a primary drainage operation has already been done); mediastinitis; hæmorrhage from paraœsophageal tissue and from spleen (Herrington et al. 1959); and, if by the thoracic route, all the complications peculiar to thoracotomy.

The emphasis in gastrointestinal surgery should not be placed upon precipitate emptying as a disease factor. It is not this which is to be feared, but rather stasis—and stasis is technically avoidable.

Summary

Malabsorption after gastrectomy is often due to stasis in the afferent duodenal-jejunal loop, and is an example of " the blind-loop syndrome ".

The causes of afferent-loop stasis are discussed, and the technical details of avoiding it are described.

Radiological diagnosis of afferent-loop stasis is discussed.

A first principle of gastrointestinal surgery is the *quiet confluence of unobstructed streams.*

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EARLY POSTOPERATIVE INFLAMMATION OF THE EFFERENT LOOP AFTER POLYA GASTRECTOMY

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THIS article reports three cases of early postoperative inflammation of the efferent loop of the jejunum following a Polya-type gastrectomy. The operative procedure was almost identical in the three cases. About five-sixths to six-sevenths of the stomach was removed. A new lesser curve was constructed by suturing the right end of the divided stomach remnant, leaving a large enough opening for a $1^1/_2$–2 in. stoma at the greater curve end. This was anastomosed to an antecolic loop of the jejunum, the afferent loop being short and related to the greater curve, and the efferent loop being related to the newly constructed lesser curve (fig. 1). Light uncovered clamps, as recommended by Burge (1956), were used, and were applied to the jejunum, keeping well away from the mesentery.

The lesser curve was supported by leaving the ligature around the left gastric artery long, and by tying it to the last suture used to attach the jejunum to the re-formed lesser curve of the stomach (fig. 2) as advised by Capper and Butler (1951) and Butler and Capper (1951). In the first patient, most of the re-formed lesser curve was covered up by suturing the first inch or so of the efferent loop to it, but in the others it was left uncovered.

In each of these cases, something had obviously gone wrong on about the fourth postoperative day. In the first two, at first, there seemed to be insufficient reason for reopening and when an operation became imperative, their condition had deteriorated so rapidly that intervention was too late. It was this experience that led to a laparotomy being done on the third patient as soon as something amiss was suspected; this patient survived.

THE FIRST PATIENT

A man, aged 26. Had been admitted three weeks before operation with an attack of severe upper-abdominal pain which was first thought to be biliary colic but was later diagnosed as due to a leaking duodenal ulcer. He was a very tensed-up artistic type of young man. A gastrectomy was done on April 12, 1951, six-sevenths of the stomach being removed. There was extensive duodenal scarring with fresh adhesions to the gallbladder and liver. The duodenum was divided, closed $1^1/_2$ in. beyond the pylorus, and a drain was placed down to the stump. After the operation he had much trouble with wind, and the stoma did not work well until the fourth day, when he had a bowel action. He continued to have some colicky pain, relieved by enemas on April 20. His pain became more constant, and on April 21 he had sudden severe pain with shock and sweating. A diagnosis of a perforation was made; a laparotomy was done; and the first 18 in. of jejunum was found to be intensely inflamed and of tissue-paper consistence. There was a series of ulcers, three of which had sloughed and perforated. The perforations were oversewn, and a free omental graft was applied. The patient did not rally, and died about six hours after the operation. A post-mortem examination confirmed the ulceration of the jejunum. The stomach and duodenal suture lines were sound. The patient was not given any chemotherapy after operation.

THE SECOND PATIENT

A man, aged 24, gave a history of four years' epigastric pain, which was shown to be due to a duodenal ulcer. On July 11, 1958, gastrectomy was performed, five-sixths of the stomach being removed. The duodenal ulcer was posterior with scarring, but was not too adherent. A duodenal closure was done. The anastomosis was completed as described (figs. 1 and 2) and

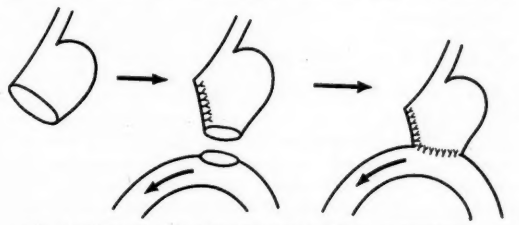

Fig. 1—Afferent and efferent loops in Polya gastrectomy.

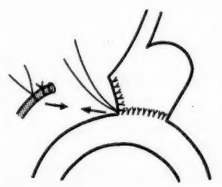

Fig. 2—Suspension of lesser curve of stomach after Polya gastrectomy.

500,000 units penicillin and 1 g. of streptomycin in 5 ml. saline were put into the peritoneal cavity before closure. The postoperative progress was normal until the night of July 13, when he had an attack of dyspnœa which the house-surgeon thought was due to asthma. On the morning of July 14, he seemed a little unwell and had abdominal distension. There was no rise in the pulse-rate or temperature. A vertical X-ray film of the abdomen showed fluid levels in the small bowel, and gas in a loop in the left hypochondrium which was thought to be the splenic flexure of the colon. By 4 P.M., he had had three motions, but the abdomen was still a little distended and was silent.

An X-ray at 7 P.M. showed fewer fluid levels in the small intestine, and more gas in the splenic flexure. On July 15, he had six motions; the abdomen was softer and only a little distended. On July 16, the diarrhœa was less. His temperature was about 100°F, and his pulse-rate 90–100. On July 17, he had five motions and on the next day the diarrhœa continued and his temperature rose to 102°–103°F. He developed a widespread bronchopneumonia confirmed by X-ray. The abdomen became distended, and an X-ray showed no fluid levels, but gas in the left colon, with a superimposed distended loop of small bowel in the left hypochondrium. Next day, the abdomen was even more distended, though peristalsis was still present. At midday, he had a small vomit of clear fluid, and his condition deteriorated. A Levin tube was passed, but only a little clear fluid was aspirated. An X-ray of the abdomen now showed only a distended loop in the left hypochondrium, which looked as if it was small bowel.

A laparotomy was performed through the previous incision.

The proximal 2 ft. of jejunum were grossly distended and inflamed, but not obstructed. There were four sloughs about 1 ft. from the duodenojejunal flexure, the longest of which ruptured as the loop was delivered. One, about 9 in. lower down, had already burst and spilled into the peritoneum. All sloughs and perforations were oversewn, or closed with two layers of interrupted thread. The distended upper part of the jejunum was decompressed with a Bruecke double-lumen tube, introduced through a stab-incision in healthy bowel wall which was closed with a purse-string suture. The rest of the small intestine was of normal size. The duodenal and stomach suture lines were healthy. 500,000 units of penicillin and 1 g. of streptomycin were left in the peritoneal cavity, and a suprapubic peritoneal drain was inserted. His condition was fairly satisfactory after operation, but he died at 2.30 A.M. on July 20. Penicillin 500,000 units and streptomycin 1 g. were given twice daily intramuscularly from July 14 to July 16. On July 18, penicillin 100,000 units and streptomycin 1 g. twice daily intramuscularly was begun. Permission could not be obtained for postmortem examination.

THE THIRD PATIENT

A man, aged 18, gave a history of twenty days' epigastric pain before admission. He was found to have a duodenal ulcer. After two weeks' medical treatment, he still required morphine injections for pain. A gastrectomy was performed on Aug. 14, 1958, when five-sixths of the stomach was removed. A chronic duodenal ulcer was found penetrating the pancreas posteriorly, and puckering the anterior wall of the duodenum. A prepyloric closure was done. 500,000 units penicillin and 1 g. of streptomycin were left in the peritoneal cavity before closure. Next day, he appeared well and a few bowel sounds were present. On the morning of Aug. 16, he passed flatus, but bowel sounds were absent and his abdomen was slightly distended. Small amounts of clear fluid were being aspirated from the Levine tube. At 5.30 P.M., he was more distended with occasional bowel sounds. He passed no flatus after a flatus tube was inserted. A vertical X-ray showed distended loops of small intestine with gas in the colon. He passed much flatus after a turpentine enema. A further vertical X-ray showed distended loops still present, and gas in the colon. At 9.30 P.M., though still distended, he passed more flatus, and had vigorous peristalsis.

Next day, Aug. 17, there was still vigorous peristalsis, and some lower abdominal distension. A considerable amount of greenish fluid was now being aspirated. An enema gave a good result, and the distension of the lower part of the abdomen disappeared. A vertical X-ray of abdomen showed a distended loop of bowel in the left hypochondrium, superimposed on a distended colon. The radiological appearances resembled those of the previous patient (case 2).

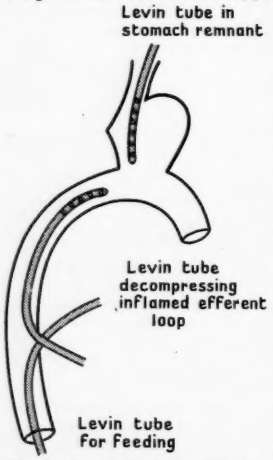

Fig. 3—Case 3. Position of Levin tubes after operation for inflammation of efferent loop.

A tentative diagnosis of inflamed, distended efferent loop was made, and the abdomen reopened. The proximal 18 to 24 in. of the efferent loop were intensely inflamed and distended, and showed multiple ulcers which had not yet sloughed. The bowel wall was very friable. An opening was made into the jejunum below the inflamed area, and the bowel was decompressed with a Bruecke double-lumen tube. One Levin tube was then passed through the opening into the inflamed proximal bowel, and one a long way downwards along the distal jejunum (which appeared normal). The opening was closed with a purse-string suture. The bowel wall was then sewn over both tubes, as in a Witzel jejunostomy. The tubes were brought out separately through stab-wounds, and the loop was attached by a few sutures to the adjacent abdominal wall. 500,000 units of penicillin and 1 g. of streptomycin in saline were left in the peritoneal cavity. After operation, hourly aspiration was applied to a Levin tube in the stomach, and continuous suction to the Levin tube in the proximal part of the efferent loop. The tube into the distal part of the efferent loop was spigoted, and the patient was given parenteral fluids and electrolytes.

After two days, $^1/_2$ oz. plain water was administered hourly by the distal tube. By Aug. 23, this had been increased to 6 pints of half-strength milk in 0·3 *N* saline per twenty-four hours, given by continuous drip, with added potassium chloride 4·5 g. daily. The bile aspirated from the proximal tube was filtered, boiled, and returned through the distal tube to the bowel. On Aug. 24, the proximal tube was removed from the efferent loop. Feeding by mouth was increased, and feeding through the distal tube was decreased daily. The distal Levin tube was withdrawn on Aug. 29. Thereafter, he was given soft solids and gradually progressed to a normal diet. The fistulæ from which the tubes had been withdrawn healed quickly. The Levin tube in the stomach had been withdrawn earlier on Aug. 25.

Discussion

The appearance of the affected loop of jejunum in these cases was similar to that of a localised necrotising enteritis. It also bore some resemblance to the appearance of the bowel after a mesenteric thrombosis. This possibility was not thought of until recently, and no note was made at operation about the arterial supply to the affected segments, though venous congestion was seen in all the cases. We have had a recent case of mesenteric thrombosis in a patient with Buerger's disease, and we were surprised at the similarity in appearance, though the segment involved was much longer. The resemblance of these cases to those reported by Watson (1958), with distension of the afferent loop, is interesting.

The operative procedure adopted in the third case was successful. Resection of the affected loop would have been very difficult in all these patients because of the upward retraction of the stomach, the uncertain upper demarcation of the segment involved, and the intense inflammatory reaction. Once necrotic ulcers have developed, or perforation has occurred, it is difficult to know whether any treatment other than resection would be successful. A plea is made for early laparotomy on all cases of Polya gastrectomy that show some definite departure from the normal course of recovery. A sudden change in wellbeing, an unexplained colicky abdominal pain, distension, and restlessness should be enough to arouse one's suspicions. Peristalsis may persist for some time, and there may be very little in the way of rigidity and guarding. The patient may be passing flatus, or even having loose motions. Abdominal distension and ileus occur much later when perforation has taken place and then it may be too late to do anything.

Summary

Three cases of early severe postoperative ulceration of the efferent jejunal loop after a Polya gastrectomy are described.

The clinical manifestations were a change in well-being, upper abdominal pain, some distension, and persisting peristalsis.

Decompression of the loop was successful in one case.

The cause of the condition is unknown and it is

suggested that it may be associated with necrotising enteritis.

I must thank Mr. W. M. Capper for permission to publish the details of the first patient; Mr. Geoffrey Darke, who performed the first operation on this patient; and Mr. Charles Bartlett, who came to my assistance at the time of the second operation.

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ASBESTOSIS AND ABDOMINAL NEOPLASMS

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IN 1953, an impression was formed at The London Hospital that women suffering from pulmonary asbestosis had ovarian neoplasms more often than other women. The occurrence of further cases led to the present investigation, which is based on a search of the records of the hospital since 1948. In that period 23 women have been inpatients with a diagnosis of asbestosis. 15 are known to have died, 4 with lung cancers and 9 with intra-abdominal neoplasms. Of these 9, 1 had an ovarian carcinoma, and 4 had peritoneal growths, possibly of ovarian origin. In the other 4, the diagnosis was carcinomatosis peritonei and, though 2 underwent laparotomy and 1 came to necropsy, no primary lesion was found. During the same period, 19 men were admitted with asbestosis. 15 of them are known to have died, including 10 with lung cancer and 1 thought to have a malignant mesothelioma of peritoneum, though there were some features suggestive of a primary bronchial neoplasm. Detailed case-histories will be given only for the 9 women with ovarian or peritoneal growths, and for the one man thought to have a peritoneal mesothelioma. Relevant details of the other cases are summarised in tables I and II, and will be briefly discussed. Many other patients with asbestosis attend the hospital, but only as outpatients, and so do not appear in the diagnostic index. Their total numbers are therefore not known.

* This work was done while the author was medical registrar at The London Hospital, London, E.1.

Case-records

Occupational histories are omitted for brevity, but will be found in tables I and II.

Case 1.—A spinster, aged 42, was admitted in May, 1951, with papillœdemic hypertension and left ventricular failure. A diagnosis of asbestosis had been accepted by the pneumoconiosis panel five years earlier and a full pension granted. While in hospital she had retention of urine, and pelvic examination revealed a swelling in the pouch of Douglas. A week later she suddenly became unconscious, with signs of a left hemiplegia, and she died shortly afterwards.

Necropsy.—Death was due to an embolus in the right carotid artery. There was no pleural effusion, but there was a narrow band of fibrous adhesions over the anteromedial surface of the

TABLE I—CASES OF ASBESTOSIS (WOMEN)

Case	London Hospital number	Present age or age at death	Years since first exposure	Duration of exposure (years)	Type of exposure	Associated disease
1	22415/50	Died 43	21	21	Asbestos grinding	Carcinoma of ovary
2	22152/49	Died 45	28	7	Asbestos spinning	Peritoneal carcinoma, probably from ovary
3	51401/49	Died 60	46	4	Asbestos spinning	" " " " "
4	14678/52	Died 49	30	4½	Carding room	" " ? ovary; ? mesothelioma
5	4709/53	Died 52	36	3	Mattress department	Carcinomatosis peritonei
6	15921/55	Died 54	38	2	Asbestos spinning	Peritoneal carcinoma, probably from ovary
7	41550/47	Died 39	23	4	Slab-making department	Carcinomatosis peritonei
8	37260/55	Died 59	34	1	Slab-making department	" "
9	50268	Died 35	..	..	Not known	"
10	17826/48	Died 66	15	1 month	Warping machine	Carcinoma of bronchus (squamous cell)
11	29339/52	Died 59	38	7	Asbestos grinding	" " " (polygonal cell)
12	22367/53	Died 45	27	4	Asbestos weaving	" " " 'atypical' cells in sputum
13	21148/47	Died 50	20	20	Mattress department	" " " (type not stated)
14	46720/49	43 (1951)	20	3	Asbestos spinning	Last seen 1951
15	16254/50	44 (1950)	25	3	Unspecified	Well, 1950
16	53494/50	57	18	13	Unspecified	Well
17	10384/53	53	21	1½	Unspecified	Well
18	20073/54	51	26	6	Asbestos weaver	Congestive heart-failure
19	20672/54	72	19	5	Sweeper in asbestos factory	Cholecystitis
20	24986/55	Died 52	33	3	Spinning department	Pulmonary hypertension; right heart-failure; carcinoma of breast
21	14093	Died 63	30	3	Mattress filler	Carcinoma of stomach
22	25864	53	17	17	Pipe lagger	Carcinoma of breast
23	41545/51	59	32	4	Unspecified	Congestive heart-failure

TABLE II—CASES OF ASBESTOSIS (MEN)

Case	London Hospital number	Present age or age at death	Years since first exposure	Duration of exposure (years)	Type of exposure	Associated disease
24	27245/56	Died 50	26	23	Cleaning ventilators	Malignant mesothelioma of peritoneum
25	22429/51	Died 60	45	45	Asbestos lagger	Carcinoma of lung (anaplastic, spheroidal cell)
26	15204/53	Died 53	5	5	Asbestos grinder	" " " (polygonal cell)
27	11207/59	Died 47	22	2	Sorter in asbestos factory	" " " (anaplastic, spheroidal cell)
28	24877/56	Died 55	7	7	Tipping asbestos	" " " (not stated)
29	38115/56	Died 65	6	6	Asbestos carter	" " " (squamous cell)
30	29223/57	Died 54	30	15	" Asbestos factory "	" " " (squamous cell)
31	19585	Died 76	34	17	" Asbestos factory "	" " " (squamous cell)
32	24926	Died 56	40	40	Boiler coverer	" " " (squamous cell)
33	2613/56	Died 53	31	18	Unloading and sawing asbestos	" " " (anaplastic, spheroidal cell)
34	42921	Died 37	18	18	Boiler coverer	" " " (polygonal cell)
35	3719/48	Died 65	15	4½ mos.	Asbestos grinder	Suppurative pneumonia; cerebral abscess
36	48234/49	56	42	42	Boiler coverer	Emphysema; congestive heart-failure
37	28817/50	Died 62	19	19	Asbestos packer	Bronchopneumonia; diabetes mellitus
38	2599/51	Died 60	40	7	Asbestos packer	Hæmatemesis from acute gastric erosion
39	5262/52	Died 60	24	4	Asbestos factory labourer	Calcific aortic stenosis
40	17399/55	49	35	6 mos.	Breaking up asbestos	Bronchitis
41	13810	56	18	9	" Asbestos factory "	..
42	23776/49	43 (1952)	25	25	Loading and blending asbestos	..

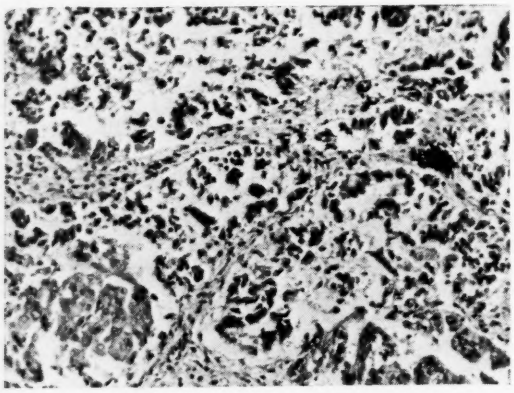

Fig. 1—Case 1. Papillary, columnar, and cuboidal-cell carcinoma, with occasional aggregates of larger, pale-staining polygonal cells suggestive of the whorling seen in squamous-cell carcinoma. (×110.)

right upper lobe. All lobes of lung showed a firm shotty induration with almost confluent nodules of greyish-black fibrosis against a paler reddish-brown background. The fibrosis was more diffuse in the anterior parts of the right upper lobe and in the right lower lobe, showing a blue-grey interlacing network of fibrous strands. The left ovary was enlarged (11 cm. diameter) by a nodular necrotic cystic carcinoma, unaccompanied by peritoneal or any other secondary deposits.

Histology.—The tumour was a papillary, columnar and cuboidal-cell carcinoma, with occasional aggregates of larger pale-staining polygonal cells suggestive of the whorling seen in squamous-cell carcinoma (fig. 1). The lungs showed peribronchiolar and peribronchial interstitial fibrosis with some slight bronchiolar epithelial hyperplasia. Numerous asbestos bodies were found, often entirely or partially ingested by giant-cells of the foreign-body type. A few asbestos bodies were found in a partially fibrotic hilar lymph-node.

Case 2.—Asbestosis had been diagnosed at the age of 40. She was admitted when she was 45, with a history of lower abdominal bearing-down pains for one year, followed by anorexia, diarrhœa and weight-loss. A large hard irregular mass was felt in the lower abdomen, arising from the pelvis. At laparotomy, the whole of the posterior sheath of the rectus appeared infiltrated by growth and no further examination was made. A biopsy was taken and histological examination showed a carcinoma composed of papillary, tubular, and cuboidal cells, suggesting an ovarian primary (fig. 2). She died in hospital after nine months.

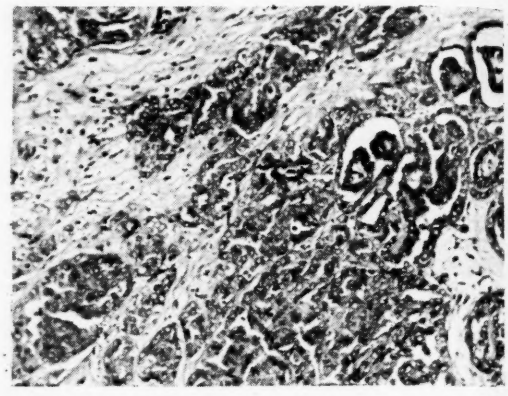

Fig. 2—Case 2. Papillary, tubular, and solid masses of cuboidal-cell carcinoma, suggesting an ovarian primary. (×114.)

Necropsy (Dr. B. E. Heard at St. Mary's Hospital).—There were many fibrous adhesions in both pleural sacs with numerous, evenly scattered, dark nodules throughout both lungs. Scrapings showed asbestos bodies. A great amount of growth filled the peritoneum and invaded the walls of the intestines, and the greater omentum. There was one nodule in the liver. The ovaries were not identified in the mass of growth filling the pelvis. The cause of death was given as carcinoma in peritoneum, probably from ovary.

Case 3.—She was found to have asbestosis in 1953, and was admitted one year later at the age of 61, with a five-week history of abdominal distension, anorexia, constipation, and progressive weight-loss. She was cachectic. There was ascites, and a large hard irregular mass could be felt rising from the pelvis. She required repeated paracentesis, and died after twelve weeks in hospital.

Necropsy.—Fibrous adhesions were found at the apex of the left lung. There was conspicuous diffuse emphysema. Asbestos bodies were seen in smears from the cut surface of the lung. Fine fibrosis was present throughout both lungs with discrete areas of anthracosis, maximal in the lower lobes. There were nodules of growth throughout the peritoneum, with plaques of growth surrounding the liver and spleen. A mass of growth filled the pelvis and the ovaries were not identified. On histological examination, the lungs showed variable pleural fibrosis. Numerous asbestos bodies were seen, with patchy fibrosis in the lung-substance. Sections of the tumour showed a moderately scirrhous solid trabecular small-cell carcinoma, with grouping of the cells suggestive of rosettes (fig. 3).

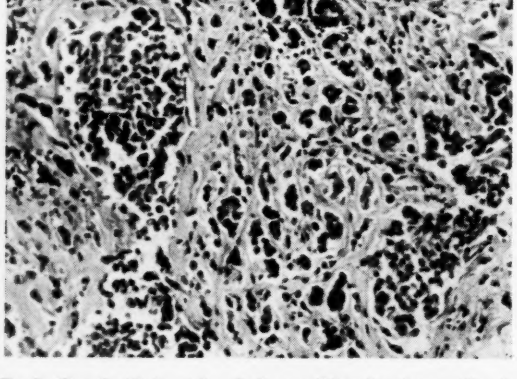

Fig. 3—Case 3. Moderately scirrhous solid trabecular small polygonal-cell carcinoma, with grouping of the cells suggestive of rosettes. (×120.)

Fig. 4—Case 4. Small cuboidal and flat celled tubular secondary carcinoma in omentum. Ovary is probable primary site, but peritoneal endothelioma is a possibility. (×114.)

Case 4.—Admitted in October, 1952, with a three-month history of abdominal swelling, weakness, and weight loss. She was ill and wasted. The fingers were clubbed. Coarse crepitations were heard at bases of both lungs. Chest X-ray showed diffuse reticulation in both lower zones with bilateral pleural thickening. The sputum contained asbestos bodies. There was ascites, and a mass was felt on vaginal examination. At laparotomy, a mass of growth filled the pelvis, and there were nodules in the omentum and over the anterior abdominal wall. A biopsy was taken, and histological examination showed a secondary carcinoma composed of small, cuboidal, tubular, and flat cells in omentum (fig. 4). The ovary was thought to be a probable primary site, though a peritoneal endothelioma could not be excluded. She was admitted on two further occasions for paracentesis, but died at home and necropsy was not performed.

Case 5.—Admitted in February, 1953, at the age of 52, with a six-week history of bearing-down pains in the lower abdomen radiating to the vagina and thighs. The pain was worse on defæcation and micturition, but there had been no change in bowel habits and no blood in stools or urine. She worked in the mattress department of an asbestos company for three years from the age of 16, and had been breathless on exertion for some years but denied having had a cough. She was ill and wasted. The fingers were not clubbed. There were bilateral basal crepitations, and X-ray examination showed pleural thickening at the right base, and fine reticulation throughout the

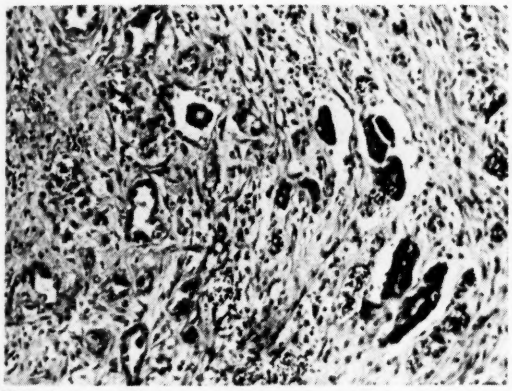

Fig. 5—Case 6. Tubular, and occasionally papillary, cuboidal-cell carcinoma suggestive of ovarian origin. (×114.)

lung-fields. The sputum contained asbestos bodies, but no tubercle bacilli or neoplastic cells. The liver was enlarged, hard, and irregular; and pelvic examination revealed a craggy mass in the pouch of Douglas. The stools contained no occult blood and a catheter specimen of urine was normal. She was thought to have peritoneal carcinomatosis and further investigations were unjustifiable. She died at home some weeks later, and no postmortem examination was made.

Case 6.—Admitted at the age of 54, when she gave a history of exertional dyspnœa for several years, severe unproductive cough for seven months and pleurisy four months earlier. Her main symptom was lower abdominal pain, associated with anorexia and weight-loss. The chest was emphysematous but there were no added sounds, and the fingers were not clubbed. Chest X-ray showed no definite abnormality, but the sputum contained numerous asbestos bodies. There was suprapubic tenderness, and on pelvic examination the uterus was felt to be enlarged, irregular, and fixed. At laparotomy, free fluid was present and the pelvis was filled by a mass of growth of undetermined origin. There were nodules of growth throughout the peritoneum. A biopsy specimen was taken and histological examination showed a carcinoma made up of papillary, tubular, and cuboidal cells, suggestive of an ovarian primary (fig. 5). She died four months later and postmortem examination was not made.

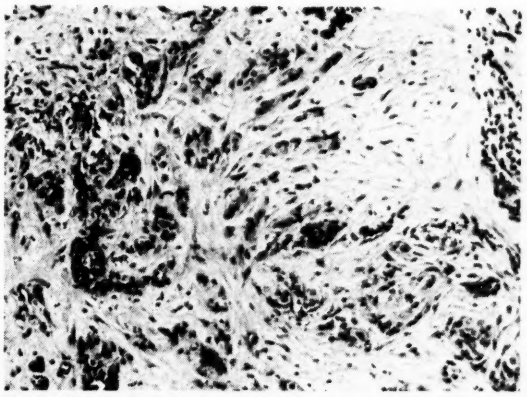

Fig. 6—Case 7. Nodule of secondary carcinoma from peritoneum, composed of solid trabeculæ of polygonal cells. (×120.)

Case 7.—Thought to have asbestosis when she was admitted at the age of 38, complaining of abdominal swelling for six weeks. She was obese and dyspnœic with impaired percussion note at both bases and bilateral basal crepitations. Chest X-ray showed diffuse mottling throughout both lungs with pleural thickening at the left base. No asbestos bodies were found in the one specimen of sputum examined. Free fluid was present in the abdomen, and a mobile mass was felt in the hypogastrium. At laparotomy, the omentum and peritoneum were studded with miliary nodules. The ovaries were cystic and studded with growth, but were not apparently the primary site. The histological appearance was that of secondary carcinoma in omentum, composed of solid trabeculæ of polygonal cells (fig. 6). She died at home six months later, and no postmortem examination was made.

Case 8.—Admitted at the age of 59. She had worked in the slab-making department of an asbestos factory for one year when she was 21. There had been no subsequent chest symptoms and the chest X-ray showed no abnormality, but her sputum contained numerous asbestos bodies. She complained of malaise for one year and of increasing girth for five months. There was gross ascites, with an irregular mass in the left hypochondrium and another in the pelvis. A barium enema showed some narrowing in the region of the splenic flexure, thought to be due to extrinsic pressure, but no intrinsic lesion of the colon. At laparotomy, the mass in the upper abdomen was found to be rolled up omentum, invaded by growth, and there were nodules of growth throughout the peritoneum. The ovaries were atrophic and also studded with growth. No abnormality was found in the stomach or intestine. The appendix and a piece of omentum were removed for histological examination, which

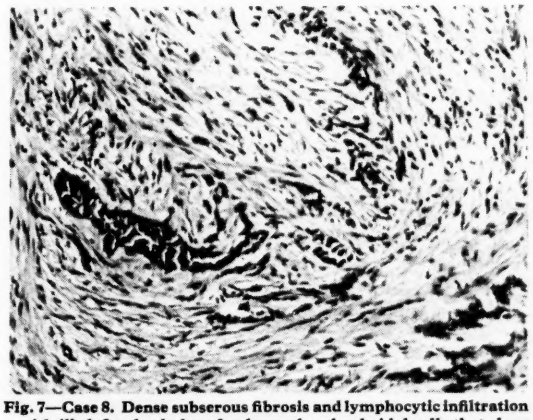

Fig. 7—Case 8. Dense subserous fibrosis and lymphocytic infiltration with ill-defined tubules of polygonal and cuboidal cells that show no cytological evidence of malignancy. (×144.)

showed very dense subserous fibrosis and lymphocytic infiltration, with ill-defined tubular inclusions lined by polygonal cells that showed no cytological evidence of malignancy (fig. 7). The patient was seen once more in outpatients two months later, when the abdomen was said to be solid with growth. She died at home shortly afterwards and necropsy was not performed.

Case 9.—A 35-year-old woman was admitted to a gynæcological ward with a three-month history of gradual enlargement of the abdomen. No history of exposure to asbestos was recorded in the notes, but her sister was noted to have died from lung cancer secondary to asbestosis. There was dullness to percussion at both lung bases, with diminished breath sounds and coarse crepitations. The abdomen was greatly distended with fluid. Chest X-rays showed loss of translucency over both sides of the diaphragm, and the sputum contained asbestos bodies. At laparotomy, hard nodular swellings were found along the mesenteric border of the small intestine and studded over the omentum. The ovaries, liver, kidneys, appendix, and uterus were normal. The patient died seven weeks after operation.

Necropsy.—A layer of soft white growth covered the visceral peritoneum over the intestines, stomach, and pelvic viscera. There was similar growth over the under surface of the left lobe

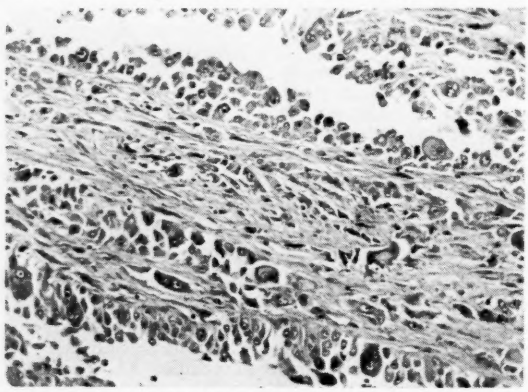

Fig. 8—Case 9. Mainly solid large polygonal-cell neoplasm with some papillary and some small-cell areas with cleft formation. A few areas show a transitional pattern. (×110.)

of the diaphragm and over the posterior adbominal wall. The ovaries were normal, but their surfaces were covered with growth. In the chest, there were tough fibrous adhesions between the right dome of the diaphragm and the lung, and two plaques of hyaline fibrosis in the pleura over the left dome of the diaphragm. No growth was found in the hilar lymph-nodes. There was diffuse fibrosis throughout the lower lobes of both lungs, with areas of confluent slaty-black anthracosis. No primary growth was found anywhere. Histological examination showed a neoplasm composed of solid, large polygonal cells with some papillary-cell and small-cell areas, associated with cleft formation. Occasional areas showed a transitional-cell pattern (fig. 8).

Case 24.—Admitted at the age of 50. Three years earlier, a diagnosis of asbestosis had been made. One year before admission, he attended outpatients with an eight-month history of epigastric discomfort, unrelated to meals but worse at night. There were no abnormal signs and a barium-meal examination showed no abnormality. He had some relief from alkalis; but vague abdominal discomfort persisted, and for two months before admission there had been loss of appetite with increasing girth. He was ill and wasted. The percussion note was impaired at both lung bases and there were bilateral basal crepitations. The abdomen was tense with fluid, but, after paracentesis, a large epigastric mass was felt. Chest X-rays showed diffuse reticulation, maximal in the lower zones. The sputum contained asbestos bodies. He died after three months in hospital.

Necropsy.—Firm fibrous thickening of the parietal pleura was present over the posterior chest wall, particularly on the right. There was slight diffuse fibrosis of the visceral pleura throughout, with underlying anthracotic flecking. The lungs showed slight diffuse induration, with scattered areas of anthracosis. No macroscopic carcinoma was found in the bronchi, or hilar lymph-nodes. In the mesentery of the ilium, a nodular firm fibrous mass was found which separated easily from the posterior abdominal wall. There were numerous nodules of growth in the lesser omentum, and around the pylorus of an otherwise normal stomach. Further nodules and plaques of growth were found throughout the peritoneum, in many places indenting the mucosa of the large and small bowel, but nowhere infiltrating the mucosa. On histological examination, the tumour shown was composed of small cuboidal cells with papillary, cleft-like, and tubular formation. There were a few areas of larger, less well-differentiated cells, and also some areas of myxomatous degeneration. This neoplasm was present in the serosa of ileum, spleen, and the peritoneal surface of the diaphragm, with one solid trabecula of cells extending through the diaphragm into the hyaline, fibrotic pleural surface. There were small clumps of cells in a carinal lymph-node, which also contained asbestos bodies. In the lungs, there was moderate peribronchiolar and pleural fibrosis with numerous asbestos bodies. A little bronchiolar epithelial hyperplasia was seen in the right lower lobe.

Discussion

Asbestosis

The first recorded case of pulmonary asbestosis was that of a patient who died in Charing Cross Hospital, London, in 1900. Details were given to the Departmental Committee on Compensation for Industrial Diseases (1907), by Dr. Montague Murray. It was not until 1930, when a further inquiry was held (Merewether 1930a and b, Merewether and Price 1930), that asbestosis was recognised as an industrial disease in this country and measures were taken to prevent it. By the nature of the work involved, these measures were unlikely to be wholly successful, and it is of interest that of the 42 cases in this series, ten (8 men and 2 women) were first exposed after 1930.

Asbestosis and Lung Cancer

Lynch and Smith (1935) reported the first case of lung cancer associated with asbestosis. In 1952, Hueper (1952) was able to collect 61 published examples. Of 99 detailed by Hueper (1955), 82 originated in England. The first statistical review was that of Merewether (1947), who reported the finding of lung cancer in 13·2% of 235 necropsies on patients with asbestosis. This was compared with an incidence of 1·32% among 6884 cases of silicosis. Wyers (1950) reported an incidence of 14·8% among 115 necropsies, and Gloyne (1951) found lung cancer in 14·1% of deaths associated with asbestosis. Doll (1955) provided further confirmation of a causal relationship with his investigation of necropsy reports on 105 persons who had been employed at one asbestos works. Lung cancer was found in 15 of 75 cases with asbestosis, and in 3 of the 30 cases without asbestosis. He concluded that the risk of lung cancer among men employed for twenty years or more was ten times that of the general population.

Such a direct association is not universally accepted. Jacob and Bohlig (1955), in Dresden, studied 343 cases of asbestosis and found only 4 cases of lung cancer, but 15 of associated active tuberculosis. They state that, during the past twenty years, the average number of asbestos workers throughout Germany has varied between 3000 and 4000 but that only 17 cases of lung cancer have been reported among them. Braun and Truan (1958) criticise statistics based on necropsy findings without reference to the popu-

lation at risk. In an epidemiological study of over 6000 workers in the asbestos mines of Quebec, they found only 9 proved lung cancers—an incidence of 25·3 per 100,000 of the population studied. Comparing this incidence with that of 22·5 per 100,000 for the rest of the province of Quebec, they conclude that the absestos workers do not have a significantly higher death-rate from lung cancer than do comparable sections of the general population.

The present series is too small for statistical analysis, but it will be seen that the incidence of lung cancer at necropsy is very much higher than any previously reported —particularly among the men, where it is 67%. This is largely explained by selection, since 6 of the 10 men were referred directly to the medical and surgical thoracic units from other hospitals with the diagnosis, either provisional or established, of lung cancer. The same explanation does not hold for the females, who all attended at general medical outpatients, thus giving a lung cancer incidence of 26% of all deaths associated with asbestosis. It will be seen from table III that the average duration of exposure

TABLE III—PERIOD SINCE FIRST EXPOSURE AND DURATION OF EXPOSURE OF 35 CASES OF ASBESTOSIS, ASBESTOSIS WITH LUNG CANCER, AND ASBESTOSIS WITH PERITONEAL CANCER

—	Number of cases		Years since first exposure		Duration of exposure (years)	
	M	F	M	F	M	F
Asbestosis and peritoneal cancer ..	1	8	26	30·7* 21–38†	23	5·8* 1–21†
Asbestosis and lung cancer	10	4	24·6* 5–45†	25* 15–38†	14·3* 2–45†	9·7* 1/12–20†
Asbestosis alone (living)	4	9	30·0* 18–42†	23·5* 18–33†	19·1* 1/6–42†	7·2* 3–17†

* Average. † Range.

of the 4 women with lung cancer was only about nine and three-quarters years whereas the average period from first exposure to death was twenty-five years, suggesting that time of exposure is not the most important factor in the development of lung cancer. Merewether (1947) also noted that the average age of death with asbestosis and carcinoma of lung was about fifty-two years against about forty-four years for those with asbestosis alone, though there was little difference in the duration of exposure. Hueper (1951) draws the conclusion that many of these patients die from asbestosis before their lung cancers have time to develop.

As in other reported series, there is no great preponderance of any one cell type. Of 15 lung cancers, 5 were squamous, 8 anaplastic, and in 2 others the type was not stated. It is worth noting that the 4 women with lung cancer were all nonsmokers.

Asbestosis and Peritoneal Cancer

Leicher (1954) reported the case of a 53-year-old asbestos worker who had suffered from asbestosis complicated by pulmonary tuberculosis for several years, and who died in 1952 from tuberculous meningitis. At necropsy, the peritoneum was found to be studded with nodules of growth and there were plaques of growth over the peritoneal aspect of the diaphragm. This was thought to be a " primary cortical cell tumour of the peritoneum ". No typical asbestos bodies or fibres were seen in the tissues of the tumour, but asbestos was demonstrated there by X-ray-diffraction techniques. Bonser et al. (1955) appear to have made the only previous reference to a high incidence of abdominal neoplasms associated with asbestosis. Out of their series of 72 cases, 4 (1 man and 3 women) had peritoneal cancers. Of the 3 women, 2 had been thought to have ovarian primaries (Bonser 1959).

TABLE IV—CAUSES OF DEATH OF 15 MEN AND 15 WOMEN WITH ASBESTOSIS

—	Men	Women
Ovarian or peritoneal cancer ..	1	9 (*60%*)
Carcinoma of lung	10 (*67%*)	4 (*26%*)
Pneumonia	2	..
Other causes	2	2

In the present series, 9 of 15 deaths in women were associated with ovarian or peritoneal cancer, an incidence of 60%. In one case (no. 5) the diagnosis was only clinical, and there was nothing in the history or examination to incriminate any particular organ as the site of the primary lesion. In the remaining 8 cases, either laparotomy or postmortem examination was performed. Only 1 (case 1) had a definite ovarian neoplasm without peritoneal involvement. In every other case there was diffuse peritoneal growth with ascites. In 4, the pelvis contained a mass of growth and the ovaries were not identified. In 2 other cases, the ovaries were said to be studded with growth but were not, apparently, the site of the primary lesion; in 1 case the ovaries were cystic but not involved by growth.

Case 24 was the only man to show a similar picture of diffuse peritoneal cancer. An intensive examination revealed no macroscopic evidence of a primary growth, but subsequent microscopy showed bronchial epithelial hyperplasia in the right lower lobe, and tumour-cells in a hilar lymph-node. In addition, there was a solid trabecula of growth extending through the diaphragm, which may have arisen on either the pleural or the peritoneal aspects. In this case, and in case 9 where plaques of growth were also found on both aspects of the diaphragm, the possibility of a missed bronchial primary is more difficult to refute.

It is possible that these cases do not represent a new pathological entity but are all cases of secondary carcinoma from bronchial primaries. The occurrence of secondary deposits from bronchial carcinoma, many months before there is clinical or radiological evidence of the primary lesion, is familiar to all. Even at necropsy, a small primary growth in the wall of a peripheral bronchus is easily missed unless specifically sought. The absence of clinical or radiological evidence of lung cancer in the 10 cases of peritoneal cancer described does not eliminate this possibility, nor will the negative record of such a primary entirely convince the sceptical. Yet the findings differ from those usually associated with carcinomatosis from lung cancer in which it is common to find deposits in liver, adrenals, and kidneys, but most unusual to see diffuse peritoneal involvement without such deposits. However, Bonser et al. (1955) and Bonser (1959) attach importance to the plaques of hyaloserositis tethering the base of the lung to the upper surface of the diaphragm in many cases of asbestosis, as in case 9 and case 24 of this series. They consider that the consequent alteration of lymphatic drainage of the region offers a means of spread to the abdomen of cancer arising in sequestrated bronchial epithelium. On the other hand, this explanation is difficult to relate to the predominance of women in the present series, since lung cancer is commoner among the men.

2 of Bonser's 3 patients with asbestosis and peritoneal cancer were thought to have primary ovarian growths. Case 1 of this series was undoubtedly ovarian, and, in 4 others, the ovaries were involved in a mass of growth filling the pelvis and may well have been the site of the primary lesion. In all cases, the histological findings have been compatible with ovarian carcinoma and this has been

the diagnosis in most cases. In spite of this, and of the fact that all but one of the cases in this series have been women, some doubt must be cast on this diagnosis. In 3 cases in which the ovaries were identified they appeared not to be the primary site, and, though ovarian carcinoma is the commonest cause of undifferentiated peritoneal cancer in women, it is possible that these organs have become a dumping-ground for other cases of "carcinomatosis peritonei" in which no definite primary can be demonstrated.

Wyss (1953) reported the findings of asbestos fibres in the urine of patients with asbestosis. Stovin (1959) found asbestos bodies in the thyroid of case 38, at necropsy, and Bonser (1959) states that asbestos fibres were found in the spleen of one of Stewart's cases of asbestosis. These were chance findings and it is possible that more diligent search, such as that of Leicher (1954), might produce further evidence of a hæmatogenous spread of asbestos fibres and their eventual deposition in extrapulmonary tissues. It is beyond the scope of this article to review the evidence for "chemical" versus "mechanical" carcinogenesis in asbestosis, but there is much support for the former concept. If this be accepted, it is conceivable that peripherally deposited asbestos may provoke local neoplastic change. McLaughlin (1959) has described a carcinoma on a doctor's finger at the site of penetration by asbestos fibres.

It remains to be explained why the peritoneum should be so frequently involved without any reported increase in other extrapulmonary neoplasms. Primary mesothelial tumours are rare, and even the concept of "pleural mesothelioma" has now been largely abandoned in favour of lymphatic spread from an underlying bronchial neoplasm or primary growth elsewhere (Smart and Hinson 1957, Hinson 1958). Hugh-Jones (1960), however, suggests that this type of tumour is more common in patients with asbestosis. Vorwald et al. (1951) suggested a mechanical factor, related to length of fibre, in the production of asbestosis; and in the course of their experiments on rats were able, by injecting asbestos fibres, to produce a fibrotic reaction in the peritoneum, but not in liver, spleen, or subcutaneous tissues. They attributed this to movement taking place between peritoneal surfaces. It has been suggested that such fibrosis may play a part in the development of neoplastic changes, and this is supported by the recent work of Menkin (1960), who produced evidence of a growth-promoting factor in inflammatory exudates and suggested that this may act as a cocarcinogen. Such a factor, together with the "chemical" factor in asbestos, may determine selection of the peritoneum as the site of tumour-formation following the transdiaphragmatic or hæmatogenous spread of asbestos fibres. To support this theory it would be necessary to demonstrate the earlier stage of peritoneal inflammation in patients with uncomplicated asbestosis. The further difficulty of the great predominance of women with peritoneal cancer in this series might be explained by the greater disposition of men to lung cancer, whether this be related to sex, associated bronchitis, smoking habits, or air pollution. It will be seen that the average period after first exposure for the 14 patients with lung cancer was under twenty-five years compared with thirty years for the group with peritoneal cancer.

It is clear that no single satisfactory explanation for these cases can be drawn from the available material, though they appear to form a clinical entity of statistical significance.

2 cases in this series require further comment. In case 8 there was a clear history of exposure to absestos dust, and her sputum contained asbestos bodies thirty-three years after exposure ceased. In spite of this, she had no chest symptoms; X-rays of her chest showed no definite abnormality, and she could not be said to have asbestosis. From the clinical course and operative findings there can be little doubt that she had peritoneal cancer. In a similar way case 27 developed lung cancer with asbestos bodies in his sputum twenty years after removal from exposure to asbestos dust, without any intervening symptoms or radiological changes to establish a diagnosis of asbestosis. Clearly the question of chemical carcinogenesis, whether it be due to the asbestos itself or to some product of its reaction with the tissues, is of medicolegal interest in these cases. In the past, Hueper (1951) has commented on "the apparent dependence of cancerous changes in the lungs of asbestos workers upon the presence of asbestosis".

Summary

23 female and 19 male cases of asbestosis are summarised with details of type and duration of exposure, period since first exposure, and associated disease.

Of 30 deaths (15 men, 15 women), there were 14 who died with lung cancer—10 in men and 4 in women. This high incidence among the men is partly explained by selection, but this does not apply to the women, who were all non-smokers.

9 women and 1 man died with ovarian or peritoneal cancer. This appears to be more than a chance association, and spread from undiagnosed lung cancer seems unlikely. At least four of the tumours were not of ovarian origin. Some evidence of hæmatogenous spread of asbestos fibres is adduced, and it is suggested that a combination of mechanical and chemical factors may determine the peritoneum as the site of inflammatory and subsequent neoplastic change.

Attention is drawn to the occurrence of bronchial carcinoma in one patient and of peritoneal cancer in a second. The sputum of both patients contained asbestos bodies many years after removal from exposure, but there was no other evidence of asbestosis.

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THE PROBLEM OF PULMONARY EMPHYSEMA

THE MISSING LINK BETWEEN STRUCTURE AND FUNCTION

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PULMONARY emphysema has remained an enigma because of the failure to find the natural link between structure and function in the lungs. This has now been realised, and more information is being sought on the form and function of pulmonary structures. Long ago, we proposed a new concept of the relationship, on the basis of which emphysema can be interpreted as pulmonary insufficiency.

Since then, much new evidence has appeared that the terminal structures of the lungs in vivo have activities such as we postulated—activities which have previously remained unnoticed in studies of dead organs. Although our views are still largely hypothetical, there are sufficient data for a new approach to the problem of emphysema.

Past and Present Hypotheses

Laennec was obviously aware of the need to explain pulmonary emphysema by a link between structure and function. He named the disease for the distended airspaces which he believed to be its essence. Considering the state of knowledge in his time, it was natural for Laennec to believe that the visible movement in breathing is the sole function of the lungs. He believed that emphysema was most reasonably explained as the mechanical effect of obstructed breathing.

Laennec conceived of a special type of inflammation causing obstruction in the bronchioles. Villemin logically speculated about a special affection of the myoelastic structures concerned with the failing elastic recoil of the lungs. The majority of pathologists and clinicians since Laennec have continued to discuss various morbid changes of acquired or inherited origin in the different component structures (vessels, bronchi, connective tissue fibres) which lead to their weakening by destruction or atrophy, and so lay the lungs open to mechanical distortion of its architecture by forces of breathing. Since the major force in breathing is exerted by the bellows mechanism of the thorax, it was only natural that many observers looked upon changes in the thoracic bone structures as the primary cause of emphysema.

In modern times, the trend has been to return to Laennec's idea of bronchial involvement as the primary cause.

Some observers speak of an active function of the bronchi disturbed by a variety of agents—infection (McLean 1958), allergy (Lister 1958), or toxic damage by air pollutants (Heppleston 1954). Bronchial dysfunction is assumed to be the factor in overdistension of air spaces by air trapping due to collapse of bronchioles, collateral ventilation, and the mechanical effects of disturbed breathing. Some observers (Dayman 1956) object to the assumption that active bronchial function is superfluous since the mechanical effects of disturbed breathing—air trapping and its sequelæ—are well explained even without active function of the bronchi.

In these pathogenetic concepts, the only common denominator is the lung conceived as primarily an organ of motion, the mechanics of which are such that, when they are disturbed, distortion of its architecture results. This takes the form of emphysematous distension of the air spaces. It has long been recognised that practically all affections of the lungs can cause this. The multiplicity of potential origins became so bewildering by the turn of the century that Hoffman (1904) stated that emphysema, as a primary idiopathic disease of uniform ætiology, was a mere myth. Now, half a century later, Liebow (1959) again points to the futility of seeking for a single cause. Yet the myth of primary emphysema continues to survive. Chronic bronchiolitis and bronchitis of insidious origins and subclinical progress are supposed to initiate the mechanical pathogenesis described.

All this time, pulmonary physiology has been concerned with measurement of ventilatory turnover of air, and of breathing capacity, with measurement of the forces involved in breathing, with compliance of the structures of the lungs and chest, and with measurements of resistance to air flow in the airways. These parameters of breathing and ventilation are usually equated with lung function proper, particularly in reference to emphysema. Pulmonary physiology can be said to have grown out of the study of emphysematous patients. In them, disturbed ventilation is an early manifestation which lends itself to exact measurement. This favoured the equation of ventilatory activity with pulmonary function, and tended to confirm the mechanical concept. Thus modern physiology has promoted the survival of Laennec's ideas, and perpetuated the belief of the lungs as an organ of motion. These beliefs are responsible for the failure to solve the problem.

It is remarkable that such concepts of Laennec have survived in spite of a century and a half of increasing knowledge of pulmonary medicine.

Adherence to the mechanical concept of lung function and of emphysema has mainly been responsible for failure to relate this disease to the primary function of the lungs —namely, gas exchange. Modern physiology has not neglected the study and measurement of pulmonary gas exchange. Ingenious gas analytical techniques have been elaborated, and are used to measure gas diffusion-rates and pressures. Abnormalities in gas exchange are now attributed to impaired ventilation and circulation, and are interpreted mostly in terms of impaired distribution of these through all parts of the lungs.

The prevailing teaching is that gas diffusion in the lungs is determined solely by the efficiency of ventilation and by the blood-flow in the alveolar capillaries. The ultimate factor in controlling the surface available for gas diffusion is presumed to be the efficiency of the cardiocirculatory pump. Since gas diffusion is a purely physicochemical process, the structures of the surface over which diffusion takes place are denied any active role in this function. The structures of the vast diffusion surface are assumed to serve only as a medium through which the gases pass, as through any other inert medium. The possibility that these structures could play an active role in the regulation of the diffusion surface has been overlooked, in spite of increasing evidence of frequent diffusion differences which cannot be explained by altered ventilation or circulation. In a large group of pulmonary diseases, gas diffusion is impaired, even though ventilation and circulation are increased. For these, the term " alveolar block due to organic tissue changes " has been conceived as an explanation to emphasise the wholly passive role of the diffusion surface. Recent studies, however, have revealed many instances of reduced diffusing capacity without such changes in the alveolar structures, and with normal ventilation and circulation. Indeed, this has

been a most common finding in so-called non-obstructive emphysema (Rappaport and Mayer 1954).

Loss of diffusion surface in later life—and often, too, in the relatively young is an unexplained finding. Frequent discrepancies between efficiency of breathing and diffusing capacity have greatly increased the breach in the concept of the lung as an organ of motion. This hypothesis no longer suffices to explain abnormalities in lung function. If we consider that the ultimate function of the lungs is concerned with diffusion of gases across the surface membrane, the structures of which are not involved in the movements associated with pulmonary ventilation and circulation, we are forced to conclude that the concept of the lung as an organ of motion has never been based on a natural link between structure and function. To find that link we must conceive an active role of the structures of the surface membrane in the maintenance of extent and quality of the diffusion surface.

Structure and Function of the Diffusion Surface

It has often been said that the bodily organs are miracles of biological engineering in that structures are adapted to their specific functions. This biological process is seen at its best in the lungs, the structures of which are wonderfully adapted to their primary function which is to create surface for diffusion of gases. Gas diffusion calls for a surface of extraordinarily large extent and yet of extreme delicacy—i.e., the largest possible surface of exposure with the least possible amount of tissue interposed between air in air spaces and blood in capillaries. The lungs consist of a vast number of airsacs, endowed with the capacity to create an internal surface the size of about half a tennis-court—a surface of such exquisite delicacy that its thinness is said to be unequalled in the body, a surface constantly recreated in form of a semifluid film, even while the frame structures of airsacs, bronchioles, and vessels retain the high degree of mobility required for ventilation and circulation.

Although the bulk of the lungs consists of air, they appear to the eye as solid organs because the air is contained in a vast number of tiny airsacs. These are generally thought of as small balloons, alternately inflated and deflated by the bellows mechanism of breathing. There is evidence, however, that these tiny airsacs take but little part in expansion and retraction of the lungs, and that the large volume changes occur in centres of airsacs in the millions of ducts and bronchioles (Hartroft 1945). Most of the lung volume is ventilated by molecular diffusion, which presumably begins at the bronchiolosaccular junctions (Roos et al. 1955).

The arrangement of the lung appears to be that of a vast honeycomb. Crowding of a prodigious number of airsacs into a small space is accomplished by infinite dividing and subdividing. Enormous increase of internal surface is accomplished by partitioning—i.e., alveolisation within airsacs. Creation of diffusion surface in airsacs goes even beyond this. The alveoli have an exceedingly rich network of capillaries of very fine mesh. These capillaries are endowed with " erectile activity " and, when filled with blood, bulge forward into the airspace (Rappaport and Miller 1938, Jäykkä 1957). This is made possible by the special nature and activity of the alveolar lining membrane, which consists of an exceedingly delicate diaphanous jelly-like film of changeable quantity and consistence. The substance for this membrane, secreted by special types of cells placed at the junctions of airsacs and bronchioles, has the unique power of reducing the surface tension to near zero (Bremer 1938, Macklin 1954, Pattle 1958). Surface tension over the curved surface of the tiny airsacs would otherwise be so high that they would contract, and would require a many times greater force of thoracic traction to keep them patent.

Creation and maintenance of diffusion surface by activities of terminal lung structures was postulated by one of us (I. R.) many years ago, and was recently described again as " visceral lung function " (Rappaport 1954). Much evidence in recent experimental and pathological work supports this view (Radford 1959, Clements 1958, Hayek 1956).* So far, only a beginning has been made in discovering the function of the ultimate structures, but we already have one testing method which affords at least an approximation of this function. On the assumption that " visceral function " operates in diffusing-surface creation and maintenance, it may be inferred that diffusing-capacity determinations may afford an approximate estimate of extent of this surface. As already indicated diffusing-capacity changes are quite independent of changes in ventilation. Breathing capacity is often high when diffusing capacity is low, and vice versa. These tests obviously measure different categories of function rather than different phases of lung function. When more is known about the nature of this, it is conceivable that chemical assay of enzyme-activating or hormone-activating cells that secrete the substance for the constantly flowing membrane of diffusion surface may afford a more precise estimate of " visceral lung function ".

We may conclude, therefore, that ventilation serving to refresh air in the lungs is an auxiliary function. Diffusion-surface creation is the primary function of the lungs. The alveolocapillary interface is an extraordinary surface constituted by unique structures which are actively engaged in constant maintenance and adaptation of diffusion surface. " Visceral lung function " refers to activity of these structures in constant creation of diffusion surface, and in autonomic regulation of the quality and extent of this surface in accord with momentary requirements for gas exchange. There is ample evidence of autonomic function of the bronchiolosaccular structures, which may be reasonably interpreted as serving the constantly changing living diffusion surface. The lungs are provided with an enormous reserve of airsacs sufficient for the needs of severe exertions in which function must be greatly increased. We postulated that during basal conditions of resting function, only a minimal extent of surface-creating activity continues in some only of the airsacs, not all of which function at one time.

Homœostatic correlation of the function of pulmonary, cardiac, and chest bellows with ventilation and circulation in the lungs has long been established. One of us (I. R.) postulated also the existence of homœostatic regional correlation of ventilation and perfusion throughout all parts of the lungs as indispensable to its visceral function. The fact of autonomic control of regional function has been confirmed in recent physiologic studies (Euler 1957). This supports our assumption that airsacs in which visceral function has ceased for any reason are also shunted from ventilation and circulation. This applies to alternation of function in the airsacs from rest to exercise under normal conditions, as well as under pathologic conditions

* Lack of space permits only a sampling of references to recent work on activities of the alveolar surface membrane structures. The literature on this is already extensive and has been rapidly increasing.

in which whole lung areas are eliminated from function which must be taken over by the intact parts of the lungs.

The problem in emphysema now becomes one of working out its evolution from " visceral dysfunction " in an increasing number of airsacs to " pulmonary insufficiency " in the whole of the lungs.

The Evolution of Pulmonary Emphysema

Emphysema evolves from " airsac emphysema " to emphysema involving the lungs as a whole, and so becomes a manifestation of pulmonary insufficiency in the strict sense of this term.

The basic lesion in " airsac emphysema " is the damaged airsac which ceased to function in diffusion-surface creation leaving only shallow vestiges of alveolar septi. This change is functional, implying failure of " visceral function "—i.e., creation of diffusion surface as outlined above. Non-functioning air spaces, enlarged by coalescence of alveoli and kept open by thoracic traction, become subject to mechanical enlargement by air trapping and collateral ventilation due to two factors: (1) the effect of thoracic traction up to a certain point is the greater the larger the air space (Head 1951), and (2) enlargement of airspaces leads to relative airway obstruction. The lumina of fine bronchioles are not widened apace with enlarging air spaces, and, the larger the air space, the relatively narrower its inlet bronchiole becomes. Thus, air space enlargement and airway obstruction are both natural consequences of " airsac emphysema ". Failure of visceral function in individual or in groups of airsacs, with its consequences of mechanical enlargement, result in *anatomical emphysema*. This may involve many airsacs in certain parts, or may be widespread over the lungs.

Failure of visceral function in individual airsacs or in groups of them may result from any damage to their delicate structures. This includes the whole gamut of infections—allergic inflammations, and toxic (physical or chemical) agents which reach these structures either by the blood-stream or by inhalation (fine aerosols). It is clinically established that, in acute damage, the visible pulmonary infiltrations may completely resolve, yet leave the delicate structures permanently injured so that emphysema may appear abruptly (Rappaport 1955). Chronic inflammatory processes and long-continued toxic damage are more apt to result in fibrotic obliteration of lung tissue. If these are extensive, and pulmonary reserve becomes exhausted, they lead to emphysema in the unaffected part of the lung by way of compensatory hyperfunction.

Failure of visceral function may also result from long-continued and excessive compensatory hyperfunction in lung areas in which available reserves of functioning airsacs have become inadequate. This is often seen to develop after resections of whole lungs, or large parts of both lungs, when the remainder lacks adequate reserves for compensatory function. In principle, this in no way differs from emphysema which develops in remaining unaffected parts of the lungs in the great variety of diseases which render functionless increasingly large proportions of available reserves of airsacs. The term " compensatory emphysema " has previously been applied to the overexpansion of unaffected parts of the lung which were engaged in truly compensatory function. At the present time, the term " compensatory emphysema " is applied to describe the failure of compensation in areas unaffected by the primary pulmonary disease or remaining after resection of large parts of the lung. There is reason to believe that interference with ventilation and circulation is here a factor in eventual failure of visceral function in airsacs long burdened by excessive compensatory hyperfunction. We have observed development of emphysema in lung areas where circulation has changed from venous to systemic arterial blood-flow by way of collaterals from bronchial or pleural arteries. Essentially the same principle is involved in so-called " unilateral emphysema " which develops on the basis of hypoplasia of a branch of the pulmonary artery (Belcher et al. 1959).

Finally, we have postulated that pulmonary emphysema may also develop on basis of " lung defects " of postnatal developmental origin (Mayer and Rappaport 1953). From our clinical observations, we are convinced that there are cases in which the condition cannot be traced to pre-existing disease of any type and that some are particularly disposed to develop emphysema early in life as a result of trivial exposures, which do not so affect the vast majority of people similarly, or more severely, exposed. This disposition is due to pre-existing defects in the lungs of postnatal developmental origin.

To understand the evolution of chronic pulmonary emphysema, we must constantly bear in mind that the lungs consist of a vast number of airsac units which can all function together when necessary, but can also function separately and compensate one another in function. In every chronic pulmonary disease, regardless of origin, the affected lung units will be temporarily or permanently out of function, and this will be compensated by the function of remaining unaffected units. Emphysema is no exception to this, and, throughout its evolution, consists of combination of non-functioning overdistended units (irreversible anatomical emphysema) and compensating units which may show evidence of reversible overexpansion according to temporary need of compensation.

Emphysema refers to the whole overdistended state of the lungs. This always includes the combination of overdistended non-functioning units (anatomical emphysema) and overexpanded compensating units in greatly variable proportions. The greater the proportion of non-functioning units (anatomical emphysema), the more need there is for compensation by functioning units involving their overexpansion which may or may not be reversible depending on the need. The more advanced the emphysema, the less reversible the overexpansion; but even then it represents the most complex mixture of non-functioning decompensated airsacs and hyperfunctioning compensating airsacs. The degree of pulmonary insufficiency is determined by the ratio of one to the other.

Continued mechanical overdistention and coalescence of non-functioning airsacs plays an important role in aggravating the emphysematous state. The mechanical factors involved include: (1) increased effect of thoracic traction on non-functioning airsacs enlarged by coalescence of alveoli, (2) progressive loss of elastic recoil, (3) collapse or compression of bronchioles, (4) complicating bronchial inflammatory processes aggravating airway obstruction, and (5) combinations of any of these. Progression of emphysema by these distending factors is quite irregular, depending on local influences determined by the primary pulmonary disease or on subsequent complicating local infections. Mechanical overdistension is thus inseparable from the emphysematous state, and greatly aggravates it by increasing encroachment upon available space in the chest and upon functioning parts of the lungs. This

mechanical part of the emphysematous state incidental to, though not inherent in, the process by which emphysema originates, contributes importantly to the progression of pulmonary insufficiency.

Compensatory lung function implies that ventilation and perfusion are diverted from non-functioning to functioning airsacs. The air contained in non-functioning airsacs must be obtained by diffusion or collateral ventilation by way of enlarging pores (Cohn) or by way of channels of Lambert (Lambert 1955). In the absence of normal perfusion from pulmonary arterioles, the blood circulation of non-functioning airsacs must be derived from systemic (bronchial) arterioles. When large parts of the lungs have become non-functioning airsacs, the shift to systemic circulation is greatly increased and pressure in the pulmonary circulation as a whole rises in proportion. Presumably this becomes the chief factor in development of cor pulmonale (Rappaport and Mayer 1957).

Summary

The problem in emphysema is, in final analysis, that of the function of the lung structures proper. In lay terms the question is whether we are " winded " or " lunged ". Past and current concepts have identified lung function with its activity in breathing. Therefore emphysema became a matter of " shortness of breath ". We conceive lung function to be a matter of the creation of diffusion surface by the activity of the structures of its innumerable airsacs, best described as " visceral function of the lungs ". This implies that lung function is determined by the available supply of airsacs and the functioning efficiency of these in the maintenance of a diffusion surface adequate in extent and quality in accord with changing requirements of the body. In lay terms this means that we are " lunged ", not just " winded ".†

Emphysema is conceived as a manifestation of pulmonary insufficiency in the strict sense. It implies inadequate diffusion surface for gas exchange either because of *insufficient number of airsacs* available for normal " visceral function ", or because of *inefficiency of their function* in maintaining adequate diffusion surface. In the origin of pulmonary insufficiency these two possible causes are so closely linked that it is hardly ever possible to make sharp distinction between them. It lies in the nature of visceral function that, as the proportion of functioning airsacs is reduced below a critical point, the function of remaining airsacs becomes increasingly inefficient with diminishing reserves.

Emphysematous changes are inherent in the evolution of pulmonary insufficiency due to functional as well as to mechanical causes. Clinically pulmonary insufficiency always consists of variable combinations of anatomical and clinical emphysema, in which a complexity of functional and mechanical factors, acting in a vicious cycle, continue to aggravate the emphysematous state by coalescence and overdistension of non-functioning, as well as by over-inflation of compensating airsacs.

† After this article was submitted for publication we noted Dr. Roger Bannister's paper presented to the Association of Physicians of Great Britain (Bannister, R. G., Cotes, J. E., Jones, R. S., Meade, F. [1960] *J. Physiol.* **152**, 661). Dr. Bannister has found that athletes have higher diffusion capacities, which affords them a higher rate of transfer of oxygen in the lungs. He concludes that increased lung-diffusion capacity is more important than muscularity, exceptionally high cardiac output, or an extra large vital capacity. This is indeed what we are implying in the above phrase, " we are ' lunged ', not just ' winded ' ".

References at foot of next column

T-SUBSTANCE ANOMALY
AN INBORN ERROR OF PURINE METABOLISM

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THE child described here excretes a previously unknown substance in his urine. This substance—provisionally named T-substance—has since been found in the urine of some of his relations. Its exact nature is not finally determined, but it appears to bear a close chemical resemblance to alloxan. It was discovered by urinary paper chromatography, done as part of an investigation of the cause of the child's physical and mental retardation, and is usually excreted in large amounts. Subsequently it has been found in similar quantities in the urines of a five-year-old child, with delayed physical development but normal mentality, and in the urine of her brother who is normal. Paper chromatograms of the urine of a mentally and physically backward infant of twenty months showed two similar spots. This patient will be the subject of a later communication.

Studies of the family of the first child are presented, and it will be seen that, inferentially, the abnormality of metabolism is transmitted as an autosomal recessive characteristic.

A brief account of the chemical investigations in this case was presented at the Fourth International Congress on Clinical Chemistry (Wilkinson 1960).

The Patient

The child was born at full term on May 19, 1955, after a pregnancy complicated by anæmia. The birth-weight was 6 lb. 5 oz. On the 1st day of life, he had a cyanotic attack, and was kept in an oxygen tent for 3 days. When he was just over a month old, he had further cyanotic attacks, and was later sent to a cardiac unit for investigation. A clinical diagnosis of Fallot's tetralogy was made; but, as he was obviously mentally

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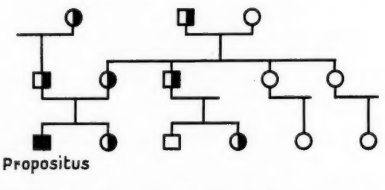
Propositus
Pigment precursor present in large quantity
Pigment precursor present in low concentration
Pigment not detected

Fig. 1—Familial incidence of T-substance.

defective, no further action was taken. During 1956, he was several times admitted to hospital because of attacks of bronchopneumonia, heart-failure, and gastroenteritis.

He first came under our care in April, 1959, when full investigations were undertaken to elucidate the cause of his lack of mental and physical development. We found that his urine contained a hitherto unknown substance—probably a purine derivative. Investigation of those members of his family from whom it has been possible to obtain urine, gave the results shown in fig. 1.

His mother says she had bilateral ptosis as a child; but this recovered spontaneously. She now has established mitral stenosis. One of his cousins, whom it has not been possible to test, is said to have bilateral ptosis. The rest of the family are well.

At 3 years 11 months, he was an active child with brown hair and brown eyes (fig. 2A and B). There was bilateral ptosis associated with backward head-tilt, but the eyes themselves were normal. He could stand alone, but could not walk unsupported. His vocabulary was limited to two or three words.

Measurements.—Head circumference, 19½ in.; crown–heel, 37 in.; crown–pubis, 21 in.; pubis–heel, 15¾ in.; ratio crown–pubis/pubis–heel, 1·27; span, 34 in.; weight, 28 lb.

Cardiovascular system.—There was a soft systolic murmur, heard best down the left sternal border, but no cardiac enlargement or alteration in heart-sounds. Femoral pulses were palpable, and the blood-pressure was 100/60 mm. Hg. No abnormality was discovered in the respiratory system or the abdomen; and muscle-tone was normal with normal tendon-reflexes and plantar responses.

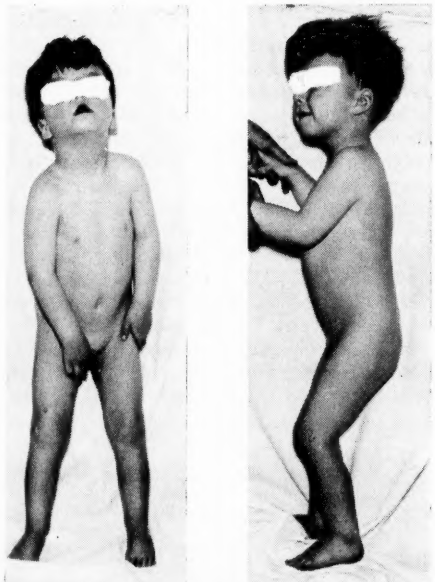

Fig. 2A and B—The patient, aged 3 yr. 11 mos.

Investigations.—Cardiac catheterisation and selective two-plane angiocardiography showed mild pulmonary hypertension, but no evidence of a shunt.

Hæmoglobin 12·0 g. per 100 ml.; white blood-cells 10,000 per c.mm. (72% neutrophils, 25% lymphocytes, 3% eosinophils). Blood-urea: 30 mg. per 100 ml. Serum-sodium 124 mEq. per litre, serum-potassium 3·7 mEq., serum-chloride 86 mEq., serum-calcium 9·2 mg. per 100 ml., serum-cholesterol 210 mg. Serum-proteins and liver-function tests: normal.

Bone-age, chest and skull X-rays: normal. Urine: faint trace of protein, but no pus cells or red blood-cells. No reducing substances found.

Urinary Aminoacids

The urinary aminoacids were investigated by paper chromatography of electrolytically desalted urine, according to the method of Bowden (1959) using quantities of urine containing 250 μg. nitrogen on a Whatman no. 1 paper.

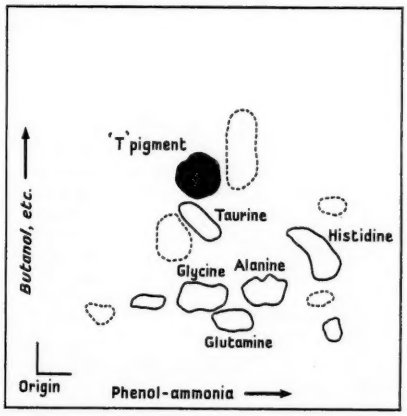

Fig. 3—Tracing of a paper chromatogram from patient's urine, showing position of pigment in relation to principal aminoacids.

Phenol-ammonia was used as the first solvent; and a mixture of butan-1-ol, butan-2-one, dicyclohexylamine, and water as the second. The chromatograms were stained with ninhydrin to locate the aminoacids. When he was first investigated, relatively large amounts of glycine, alanine, taurine, glutamine, and histidine were excreted, together with small quantities of serine and γ-aminobutyric acid. There were traces of β-amino-*iso*butyric acid, threonine, valine, arginine, and aspartic acid. Later specimens, however, showed normal patterns.

During development in the first solvent system, a reddish-purple spot, having a mobility resembling that of taurine, appeared on the chromatograms. It persisted during the run in the second solvent, in which it travelled somewhat faster than taurine (fig. 3).

In over 200 urines examined by this method, this was the first time such a spot had been seen. It persisted on a normal ward diet, free of sweets or other sources of dyes, and was not found in the urine of other patients on the same diet.

Further investigation showed that the new substance was detectable only after the urine had been electrolytically desalted, and that its colour was discharged by acetic acid but restored by ammonia. Mineral acids and caustic alkalis destroyed the material, and its colour faded appreciably during drying of the chromatograms. A second minor spot appeared when large quantities of urine were chromatographed in phenol-ammonia. Some of the major coloured compound was eluted from the chromatograms with 50% aqueous acetone, although it was not soluble in water or acetone alone. Evaporation of the eluate produced a pale-pink residue, which turned an intense reddish-

CHROMATOGRAPHIC PROPERTIES OF PIGMENT DERIVED FROM "T-SUBSTANCE"

—	Rf values obtained in parallel runs		
	Phenol-ammonia	Butanol-butanone-dicyclohexyl-amine-water (10/10/2/5)	Butanol-2N-ammonia (1/1, upper phase)
Desalted urine of patient	Major spot 0·47	(0·24) (0·42)	0·09
	Minor spot 0·81	..	..
Normal urine containing 1% alloxan (desalted) ..	Major spot 0·48	(0·27) (0·44)	0·08
	Minor spot 0·79	..	..

purple when exposed to ammonia, in much the same way as murexide.

This suggested that the anomaly might be due to a disorder of purine metabolism, and attempts were made to reproduce the formation of the coloured compounds by adding various purines and related substances to normal urines, which were subsequently desalted and chromatographed. The only substance which behaved similarly proved to be alloxan; the spots obtained were chromatographically indistinguishable from those produced by the patient's urine (see table).

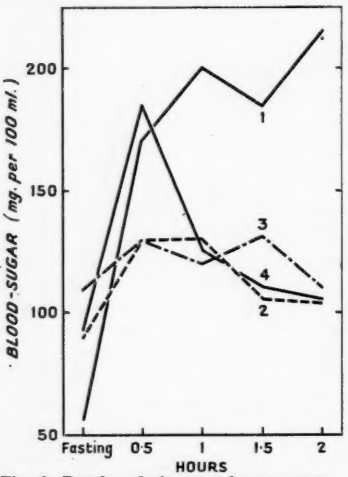

Fig. 4—Results of glucose-tolerance tests.
20 g. glucose was given at time O in test 1, but the patient refused the remainder after taking about 10 g. in tests 2 and 3. In test 4, 20 g. was given by œsophageal tube.

Because of the unexpected similarity of T-substance to alloxan, a glucose-tolerance test was carried out and gave the result shown in fig. 4 (1). Subsequent tests, however, have given completely normal curves (fig. 4—2, 3, and 4), and the child's urine has remained free from reducing substances.

Since alloxan is highly unstable under neutral and alkaline conditions it is unlikely that it would be found in urine. We have been unable to find any reference in the literature on the metabolism of alloxan in experimental diabetes to its presence in urine. Lee and Stetten (1952) reported that two-thirds of administered 2-^{14}C or ^{15}N-labelled alloxan was excreted by rats and rabbits within 3 days, but were unable to detect alloxan in the urine.

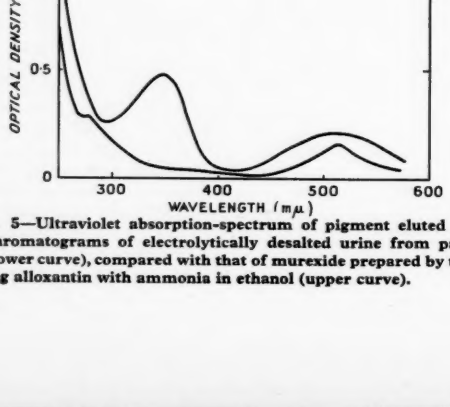

Fig. 5—Ultraviolet absorption-spectrum of pigment eluted from chromatograms of electrolytically desalted urine from patient (lower curve), compared with that of murexide prepared by treating alloxantin with ammonia in ethanol (upper curve).

Comparison of the ultraviolet absorption-spectrum of the pigment derived from T-substance with that of murexide, prepared by treating alloxantin with ammonia in 50% ethanol, showed that there is similarity in the visible region only (fig. 5). Another difference is that T-substance is extractable into n-butanol at pH 5, whereas alloxan is not. After removal of the solvent, the extract was dissolved in water and electrolytically desalted. The resulting solution gave the red spot when chromatographed in phenol-ammonia.

We tried to determine whether the abnormal substance appearing in the urine was the result of the metabolism of exogenous or endogenous purines. The child was given a virtually purine-free diet containing milk, cheese, and eggs; and the spot disappeared from his urine chromatograms. It did not reappear when the purine bases caffeine, adenine, guanine, xanthine, and the pyrimidine bases cytosine, thymine, and uridine, in daily doses of 100 mg. were added to the diet; but, when a normal diet was reintroduced, the spot returned. We are indebted to Dr. Mary L. Efron, of University College Hospital Medical School, for examining specimens of urine by high-voltage electrophoresis (Efron 1959). When the patient was first under investigation, Dr. Efron reported that no uric acid could be detected; but, in later samples of urine, small quantities were found. Subsequently serum and urine uric acid levels (determined colorimetrically) became normal, except when the patient was placed on a diet low in purines.

Discussion

Since the advent of relatively simple methods of examining the serum and urine for abnormal substances, a growing diversity of genetically determined metabolic errors has been described; there are at least 50 well-authenticated deviations (Hsia 1959). The abnormality we describe is interesting because it appears to be the first anomaly of purine breakdown, other than uricæmia. Intensive chemical analyses have not so far identified this substance, but there are good grounds for believing it is closely related to alloxan. Alloxan is an oxidation product of uric acid, and it may well be that in our case there is an abnormality in uric-acid formation which results in the accumulation of T-substance. This may have poisonous effects when formed in sufficient quantities. Two of the four subjects excreting large amounts of T-substance or similar compounds, are grossly retarded physically and mentally; a third child is small for her age, weighing only 20 lb. at 5 years. The fourth child, a brother of the last, is, as far as we can ascertain, normal in all respects other than the excretion of T-substance. The family tree of our patient shows that the abnormality is inherited as an autosomal recessive, since both parents excrete the substance in small amounts, but do not seem to be disabled apart from acquired disease. Many of the ascendants and collaterals also excrete the substance in small quantities, but without overt ill effects. The observation that females may excrete T-substance in large quantities suggests that they may also be affected, and seems to discount the possibility that the gene is carried on the X-chromosome.

An important, but still unanswered, question is whether this metabolic defect is directly related to the abnormalities observed in three of the four homozygous children. As far as we can find out, there is no other obvious explanation for their gross physical defects, and we must infer that this is the cause of their disabilities. It has been impossible, at the time of writing, to find out whether the substance excreted is present in the serum; but it probably accumulates in the blood, and there is a threshold level above which it appears in the urine. This would explain the disappearance of T-substance from the urine during the short periods in which the

child received a purine-free diet, and suggests that T-substance may be entirely related to exogenous purine metabolism.

Summary

Clinical and biochemical details of a child, aged 4, who excretes a hitherto undescribed substance in his urine are presented. This abnormal urinary constituent, still unidentified and called provisionally T-substance, is also excreted in much smaller amounts by many members of the child's family. The metabolic defect appears to be transmitted as an autosomal recessive characteristic. The child is both physically and mentally retarded.

Two other children—unrelated to the first—have been discovered who excrete T-substance in equivalent amounts and are believed to be homozygous for the abnormal gene: one of these is physically, but not mentally, retarded. A fourth child who is physically and mentally backward also excretes a similar substance.

T-substance is apparently an abnormal product of purine metabolism, chemically related to, but not identical with, alloxan.

It is a pleasure to express our thanks to Mr. D. R. W. Rawson, technician, who first drew attention to this peculiarity, and carried out much of the technical work; to Dr. C. S. Ayoub, lately registrar at Westminster Children's Hospital; and to Dr. P. V. Hunt and Dr. P. Boardman, house-physicians, for the care and hard work they have bestowed upon the patient. Also to Sister M. Parker and the nursing staff of Muriel Lesley Gamage ward, without whose skilled nursing the metabolic studies could not have been undertaken.

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ARTIFICIAL INSEMINATION (HUSBAND) IN THE MANAGEMENT OF CHILDLESSNESS

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MOST gynæcological departments in the larger hospitals in this country have special clinics for the investigation and treatment of childlessness, but little is known of the use that they make of artificial insemination with husbands' semen. There is scant information about the extent of the practice, the type of case selected for insemination, the chance of success, or the likelihood of complication. More attention has been paid to donor insemination, with its ethical and legal overtones; but, here again, there is little factual information. My own experience of insemination is not extensive, and is limited to cases in which husbands' semen has been used. Since 1946, I have examined 1400 married couples whose complaint has been involuntary childlessness. In 55 of them, artificial insemination with the husbands' semen has been given serious trial.

Technique of Insemination

The courses of insemination often extended over several months. Each course consisted of three inseminations, carried out on the twelfth, fifteenth, and eighteenth days of the cycle. The shortest course lasted two months and the longest was continued intermittently for two years.

Semen was obtained from the husbands under standard conditions. They were advised to avoid intercourse for three days before producing the specimen, which was placed directly into a small sterile glass jar, specially provided for the purpose.

TABLE I—DATA ON 55 CASES OF ARTIFICIAL INSEMINATION

Reason for insemination	No. of patients	No. of patients who conceived during treatment	Remarks
Oligospermia (spermatozoon-counts below 10 million per ml.)	34	2	8 of these patients subsequently conceived without insemination. With 1 exception all the pregnancies terminated successfully
Apparent cervical hostility	8	1	2 patients conceived some time later without insemination. All 3 pregnancies were successful
Male impotence ..	7	6	Each of the 6 pregnancies produced a normal child
Hypospadias	2	2	Both pregnancies were successful
Bilateral blockage of vasa with epididymal cysts	2	0	Spermatozoon-counts varied from 5 to 20 million per ml. in each case
Negative postcoital tests	2	2	Both husbands were highly fertile. The pregnancies were uncomplicated

In the early cases, 0·1–0·2 ml. of semen was placed into the lower part of the cervical canal. The semen was never more than two hours old. A sterile 1 ml. syringe and a long wide-bore needle with a blunt point were used for the purpose. In 1950, intracervical insemination was discontinued and thereafter 0·5–2 ml. of fresh semen was sprayed round the external cervical os. For half an hour after insemination the patient remained at rest on her back with the buttocks slightly raised.

Results

Husband and wife had previously had routine investigations carried out in the departmental infertility clinic and full medical histories were available. There were a variety of indications for insemination—some female, others male (table I).

Oligospermia

Each of the 34 husbands in this group had a spermatozoon-count consistently below 10 million per ml. and, so far as could be ascertained, this was the only apparent reason for the childlessness.

The shortest course of insemination in this group was seven months and the longest (with two months missed) was two years. 2 of the women became pregnant, the 1st after eleven months' and the 2nd after eighteen months' treatment. Both pregnancies were uncomplicated and produced normal children.

In following up this group of 34 women, it was discovered that 8 of them had subsequently conceived without insemination and that 7 successful pregnancies had resulted. Where poor-quality semen appears to be the cause of childlessness, there is nothing to suggest that insemination improves the chance of conception. Indeed, it may have the opposite effect for it is quite likely that the artificial method by which the specimen is collected may further depress the semen quality.

For the past few years in this department, oligospermia has not been accepted as an indication for insemination.

Apparent Cervical Hostility

In each of the 8 cases, repeated postcoital examinations revealed only dead spermatozoa in the cervical mucus, in spite of the fact that the husbands all had excellent semen specimens. No obvious abnormality had been found in any of the women at the infertility clinic. 1 patient conceived during treatment; another 2 became pregnant some time after the inseminations had been discontinued.

TABLE II—CLINICAL DETAILS OF 7 CASES OF MALE IMPOTENCE

Case	At time of original consultation			Outcome
	Husband's age (yr.)	Duration of marriage (yr.)	Duration of impotence	
1	28	3⅛	Throughout marriage	Conception during 3rd course of inseminations
2	36	2⅛	Throughout marriage	Conception during 7th course of inseminations
3	33	4	Last 3 yr. of marriage	Conception during 4th course of inseminations
4	26	2	Throughout marriage	Insemination abandoned after 2nd month
5	27	1⅛	Throughout marriage	Conception during 3rd course of inseminations
6	40	7	Throughout marriage	Conception during 10th month of inseminations
7	31	5	Throughout most of marriage	Conception during 4th month of inseminations

Again the results suggest that insemination, under these circumstances, does not increase the likelihood of conception.

Male Impotence

These were the most successful cases in the whole series—6 out of 7 women became pregnant by insemination (table II). The 7th husband experienced difficulty in producing a specimen of semen for insemination, and after two months decided to discontinue the attempt. All 6 pregnancies resulted in normal children. 4 of the 6 men whose wives became pregnant were subsequently able to achieve a normal sexual relationship—in 2 cases during the pregnancy, and in the other 2, within six months of the birth of the child. The following histories illustrate a number of points common to many.

THE FIRST CASE

Husband and wife were well educated and intelligent. At the beginning of the marriage, the husband experienced difficulty in having intercourse due to, he thought, the use of a sheath contraceptive. This was exchanged for a vaginal occlusive pessary, and for six months intercourse was satisfactory. The husband then began, once more, to have difficulty in achieving and maintaining an erection; and, by the end of the first year of marriage, he was impotent and had lost all desire for intercourse. Six months later he was referred by his general practitioner to a psychiatric department. He attended at intervals over the next eighteen months, and was successively under the care of four different psychiatrists. Just when he felt that he was making progress he would find himself under the care of a new doctor. At the end of eighteen months there was no improvement in the impotence.

When seen at the infertility clinic, they had been married four years. Investigations revealed no abnormality, apart from the husband's impotence. Insemination was agreed upon and conception took place during the fourth month of treatment. The pregnancy had a noticeable effect on the husband. Within three months of conception he had resumed normal sexual relations with his wife. Two years after the birth of the child, marital relations were still normal (case 3, table II).

THE SECOND CASE

Two years before marriage the husband had attempted unsuccessfully to have intercourse with another woman. He was very conscious of this failure and had no hesitation in blaming this experience for his subsequent impotence. For the first six months of the marriage he was completely impotent, but a gradual improvement took place over the next year so that he was sometimes able to effect penetration but never to achieve an orgasm. A herniorraphy operation eighteen months after marriage was followed by a recurrence of the impotence, and this continued until the couple were seen at the infertility clinic, five years after marriage. Investigations revealed no significant abnormality in husband or wife and insemination was agreed upon. Conception took place during the fourth month's course of inseminations.

The husband's impotence continued throughout the pregnancy; but, three months after the birth of their child, normal sexual relations were achieved. Nine months after the birth of this child, a normal conception took place, but this pregnancy ended in abortion at the tenth week. A year after the abortion, sexual relations were then quite satisfactory (case 7, table II).

Hypospadias

Both men in this group had severe degrees of hypospadias; and, although intercourse was possible, there was complete inability to deposit semen in the vagina. Semen quality was excellent in each case, and insemination was successful in the fourth and seventh months respectively.

Bilateral Epididymal Cysts with Blockage of Vasa

Each of the 2 men had azoospermia, associated with bilateral epididymal cysts and blockage of the epididymides. Fluid containing motile spermatozoa was obtained from these cysts and used for insemination. The 1st couple, after seven months, decided to adopt a child.

The 2nd husband was offered surgical treatment by a colleague who carried out a vasoepididymal anastomosis, but spermatozoa did not appear in the semen. Fluid from the other cyst was used for insemination over a period of ten months until the cyst fibrosed and the treatment had to be abandoned.

Negative Postcoital Tests

In both cases, routine investigations on husband and wife showed no abnormality yet repeated postcoital tests revealed no spermatozoa in the vagina. Husband and wife were adamant that intercourse was normal, and usually accompanied by a male orgasm. One couple had been married for two and the other for four and a half years. Neither husband had any difficulty in producing specimens of semen which were shown to be highly fertile. In one case insemination was successful in the third month and, in the other, in the fourth month of treatment.

A 3rd couple, similar in every way, are at present under treatment. Insemination has been going on for seven months, so far without success.

Complications

Significant complications have, on occasions, been encountered. Between 1947 and 1950, when intracervical insemination was used, several women complained of colicky lower abdominal pain for several hours after 0·1 to 0·2 ml. of semen had been placed in the cervical canal. In one or two instances the patients felt sick or vomited and had to remain in bed for twelve hours. One patient developed an acute cervicitis, and another an acute salpingitis. Fortunately, both responded to antibiotic therapy. Intracervical insemination was stopped after these two incidents and no complications have been noted since then.

Conclusions

This small series shows that insemination with husbands' semen has a limited but important place in the management of childlessness. Conception is most likely to follow insemination when husband and wife are fertile but the husband is incapable of depositing semen in the vagina. It is encouraging to find that pregnancy, under these circumstances, can help husband and wife achieve a normal sexual relationship.

Impotence can take other less obvious forms. It may appear from the clinical history that the sexual act is normal in every way, yet repeated postcoital tests show that there is no ejaculation of semen into the vagina. This type of coital failure is probably unusual; but lesser degrees, where the husband fails to ejaculate on many occasions,

may be more common than is generally suspected. Insemination will increase the likelihood of conception in these cases.

When semen quality is poor, there is no evidence that insemination improves the chance of conception. These couples are best advised to continue their normal sexual relationship; for there is good evidence that, even with severe oligospermia, intercourse can result in conception and successful pregnancy (Harvey and Jackson 1948, White and Barton 1951, Russell 1954).

I am grateful to Mr. Keith Yeates of the Newcastle General Hospital for his help in dealing with one of the men with bilateral epididymal cysts and azoospermia.

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TREATMENT OF THE NASAL CARRIER OF STAPHYLOCOCCUS AUREUS WITH FRAMYCETIN AND OTHER ANTIBACTERIALS

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THERE is general agreement that the healthy nasal carrier of *Staphylococcus aureus* constitutes one important reservoir of infection. Since many different phage-types are responsible for endemic staphylococcal disease in hospitals, it is impossible to distinguish between benign and dangerous carriers (Williams 1959). Accordingly, one is forced to regard all carriers as potentially dangerous (Elek 1959). When an outbreak of staphylococcal infection is traceable to a particular phage-type—e.g., 80/81—the detection of the dangerous disperser is greatly simplified; but this ideal epidemiological situation is seldom found in endemic hospital cross-infections affecting adults.

A reduction in the number of nasal carriers of staphylococci cannot be brought about by the use of antibacterial nasal toilet alone, as the nasal mucosæ are continually exposed to reinfection by airborne organisms. The more widespread the environmental contamination, the higher the nasal carrier-rates among staff and patients. If, however, the endemic balance between primary and secondary sources of infection could be reduced, then the chances of acquiring clinical infection should be lower—assuming, of course, that there was no change in virulence of the organism and no lowering of resistance of the patient.

We are here concerned with the treatment of the nasal carrier. We have compared a number of recommended preparations—firstly as regards the rate of suppression of nasal carriage, and secondly, the success-rate after seven days of treatment. Recolonisation of the cleared carriers was sought, but this is as much an index of environmental exposure as a measure of the efficacy of nasal toilet.

Of the two methods of applying these preparations, we have found the aqueous spray generally more effective than the corresponding ointment (or cream). Doubtless the ointment remains longer in contact with the mucosal surface, but it seldom reaches sites of possible colonisation that are beyond the vestibule of the nose.

We have always used a " deep nasal swab " for detection of nasal carriers in preference to the commonly used " shallow swab " of the anterior nares. In a survey of 103 patients, deep swabbing yielded a higher proportion of positive carriers. As the success of any preparation depends on contact with the infecting organism, deeply and liberally applied sprays must carry a greater chance of success than a cream applied to the anterior nares.

Materials and Methods

Nasal swabbing.—To have a sound basis for selecting nasal carriers, two types of swabs were taken in a group of 103 patients at the one visit. The first swab was made from the vestibule of each nostril, that is, an anterior nasal swab; and the other from the vestibule to a point just below the middle turbinate, that is, a deep swab (fig. 1). In each case the swab was rotated through three full turns during the operation of swabbing. The deep-swab technique should be done by a person familiar with the internal anatomy of the nasal cavity. All swabs were plated on blood-agar media, incubated for twenty-four to forty-eight hours at 37°C. *Staph. aureus* was identified on colony form, and on pigment and coagulase production.

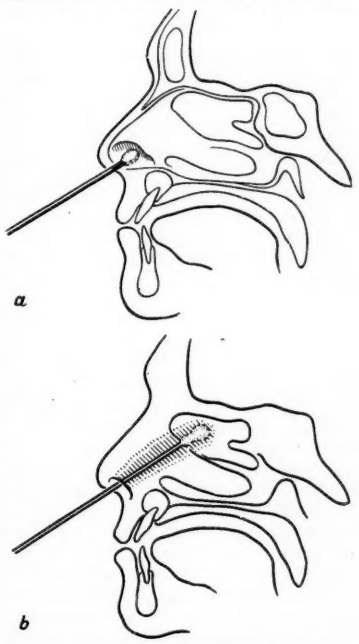

Fig. 1—*a*, area sampled in anterior nasal swab; *b*, area sampled in deep nasal swab.

Nasal preparations.—The products used were:

a. ' Neotracin ' ointment containing neomycin 5 mg., polymyxin 5000 units, and bacitracin 500 units per g.

b. ' Neomyxin ' spray containing neomycin 2 mg. and polymyxin 5000 units per ml.

c. ' Naseptin ' ointment containing chlorhexidine hydrochloride (' Hibitane ') 0·1% and neomycin 0·5%.

d. Chlorhexidine-neomycin spray in saline containing the same concentration of active ingredients as naseptin.

e. ' Soframycin ' ointment containing framycetin 1·5% and gramicidin 0·005%.

f. Soframycin spray containing framycetin 1·25% and gramicidin 0·005% in isotonic solution containing phenylephrine hydrochloride 0·25% as a vasoconstrictor.

g. Soframycin spray as (f) but without the vasoconstrictor.

The ointments were applied with a swab to the anterior nares. The sprays were instilled into the nasal cavity, under pressure, from plastic containers in such quantity that some of the liquid passed to the back of the patient's throat. All patients were treated individually by one or other of us. Each preparation

TABLE I—COMPARISON OF ANTERIOR AND DEEP NASAL SWABBING OF 103 PATIENTS IN HOSPITAL

Type of swabbing	Nasal carriers detected	
	Number	Carrier-rate
Anterior	35	34%
Deep (see text)	53	51%

was tested in 20 patients, each of whom was shown to have more than twenty colonies of *Staph. aureus* on plating of a deep swab. On every occasion, the patient was swabbed immediately before treatment, two hours after the first application, and afterwards daily for seven days. Medication then ceased, but daily swabbing was continued for at least twenty-one days, or for a shorter period if the patient was discharged from the hospital.

Results

A significant difference in the number of detectable nasal carriers can be shown after shallow (anterior nasal) and deep (anterior and middle nasal) swabbing. Table I shows the results obtained on 103 patients, and emphasises the importance of taking a deep nasal swab.

Table II summarises the results of treatment of groups of nasal carriers with the different preparations.

In this table we have listed the results obtained twenty-four hours, and seven days respectively after the beginning of treatment. The soframycin spray was outstandingly more successful after twenty-four hours than any of the other preparations. The inclusion of a vasoconstrictor in this spray appeared to improve its antibacterial action over a period of seven days. The fluted nebuliser in which the soframycin

TABLE II—RATE OF CLEARANCE OF *Staph. aureus* BY VARIOUS PREPARATIONS

Preparation	Frequency of application	Number treated	Number cleared (negative swab) after:	
			24 hours	7 days
Soframycin spray with vasoconstrictor	once daily	20	17 (85%)	20 (100%)
Soframycin spray without vasoconstrictor	once daily	20	17 (85%)	17 (85%)
Soframycin ointment	twice daily	20	5 (25%)	18 (90%)
Chlorhexidine-neomycin spray ..	once daily	20	5 (25%)	15 (75%)
Naseptin ointment (chlorhexidine-neomycin) ..	twice daily	20	1 (5%)	9 (45%)
Neomyxin spray ..	once daily	20	7 (35%)	10 (50%)
Neotracin ointment	thrice daily	20	4 (20%)	13 (65%)

spray is dispensed may contribute to its success. About 2 ml. of fluid is ejected, first as a coarse spray and then as a fine jet. On the figures recorded here, one application of soframycin spray suppressed nasal staphylococci in 85% of nasal carriers. In fact, approximately 80% of carriers are cleared within two hours of the first application of the spray. No other product in this series was so effective. Daily treatment for seven days with soframycin spray cleared all carriers in our series. Of the other preparations, chlorhexidine-neomycin spray appeared to be the next most efficacious, but was considerably less so than soframycin.

The remarkably rapid rate of clearance induced by soframycin in this series was investigated further using 85 nasal carriers, who were treated twice with the spray at twenty-four hour intervals. The results of this short treatment are shown in fig. 2.

It will be seen that 76% of the carriers were cleared within two hours after one application of the spray, and all were free of staphylococci after the second application. The antibiogram patterns of a number of staphylococci were done, and most of the strains were resistant to penicillin, streptomycin, and the tetracyclines; in other words, they were typical of the " hospital staphylococcus ".

Reinfection of the nasal mucosæ after clearance occurred with all preparations. Table III shows that approximately 50% of the cleared carriers reverted to the carrier state after cessation of treatment, but the time taken to revert after soframycin was clearly different from that found with the other preparations. With the latter, the staphylococcus free state lasted, on an average, two days, whereas after soframycin treatment an average of seven to fourteen days elapsed before reversion. Since all patients were exposed to the same degree of airborne infection, it would appear that the soframycin-treated group were reinfected from exogenous sources, whereas the reversion in other carriers was mainly endogenous. Elimination in the soframycin-treated group was bacteriologically complete, but incomplete with the other preparations. Unfortunately, phage-typing of isolates was not available to confirm this interpretation, which, if correct, provides a further reason for recommending soframycin spray for treatment of the nasal carrier.

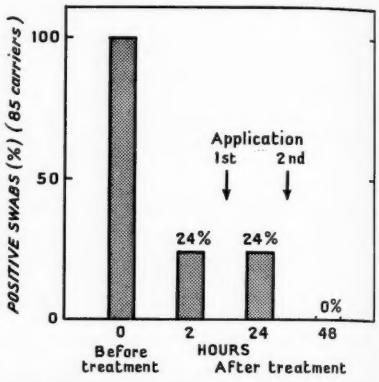

Fig. 2—Suppression of nasal carriage of *Staph. aureus* by treatment with soframycin nasal spray.

Discussion

A vast literature dealing with the nasal carriage of *Staph. aureus* has appeared during the past decade.

Some authors, e.g., Gould and Cruikshank (1957), Williams (1959) have suggested that acquired staphylococcal infections —as many as 80% of them according to Gould (1957)—might result from autoinfection. Williams et al. (1959) proved that " patients who were or became nasal carriers of staphylococci had three times as much staphylococcal sepsis as those who were never carriers ". Further, it appeared " that self-infection is important in the ætiology of the septic lesions ". In a study of postoperative surgical infections in tuberculous patients subjected to elective chest surgery, Weinstein (1959) reported that, of patients with positive nose-cultures for *Staph. aureus*, 37% exhibited postoperative infected complications, whereas

TABLE III—RECOLONISATION OF NASAL MUCOSÆ WITH *Staph. aureus* AFTER SUCCESSFUL TREATMENT

Preparation	Number of patients	Number recolonised	Average time of recolonisation after cessation of treatment (days)
Soframycin spray with vasoconstrictor ..	20	10 (50%)	14
Soframycin ointment ..	18	10 (55%)	7
Chlorhexidine-neomycin spray	15	8 (55%)	2
Naseptin ointment (chlorhexidine-neomycin)	9	4 (44%)	2
Neomyxin spray ..	10	5 (50%)	2

among the group with negative nose cultures, 11% had infected complications.

These findings suggest that the suppression of nasal carriage would be a useful measure before elective surgery, particularly in patients who are admitted to hospital some time before operation. Recent work by Gillespie et al. (1959) indicates, however, that the suppression of nasal carriage will not necessarily reduce the overall incidence of cross-infection in general hospitals. Environmental contamination can arise from primary reservoirs other than the nose—for example, the perineum (Hare and Ridley 1958), skin and clean infected wounds (Gillespie et al. 1959), all of which maintain the staphylococcal infection cycle. Silent nasal colonisation and the hazard of autoinfection inevitably follow. Nevertheless, any plan for effective reduction of staphylococcal disease in hospitals must be broadly based, and the suppression of nasal carriers by topical chemotherapy is only one of a number of measures which must be considered in the epidemiological control of this disease.

The present study was designed to provide information on an administratively simple and clinically effective treatment of nasal carriers in hospital. Thus, in comparing various preparations, it is only fair to state that we intentionally did not follow the manufacturer's directions if these were considered too complex for practical use. We were mainly concerned with discovering some preparation which could suppress nasal carriage in the shortest possible time. The test for suppression in this study was more rigorous than in most, since all observations were based on the deep swabbing technique (fig. 1). This method detected 17% more nasal carriers than swabbing the anterior nares (table I).

Soframycin spray was outstandingly the most successful preparation (table II). When a larger number of nasal carriers was treated, it was found that all carriers yielded negative cultures in forty-eight hours—that is, after two applications of the spray (fig. 2). Furthermore, it appeared that clearance of nasal staphylococci by soframycin was more complete than by other methods of treatment, since recolonisation of the mucosæ was significantly slower (table III). The success of soframycin spray is attributable largely to its bactericidal action. Experiments, not reported here, showed that soframycin killed *Staph. aureus*, resistant to many antibiotics, in less than a minute in the presence of 50% serum.

This work is now being extended to determine whether intermittent use of soframycin spray will decrease the nasal-carriage rate, and thus indirectly lower the environmental contamination. We hope that this proposed extension of the present study will provide a basis for control of the nasal carrier which does not impose too many demands on the nurses.

Summary

The treatment of the nasal carrier of *Staphylococcus aureus* by chemotherapeutic agents was investigated. The emphasis in this study was on the rate of clearance as well as the success after seven days' treatment.

The results indicate that, in general, atomised spray preparations are more effective than the corresponding ointments.

Of the preparations compared, 'Soframycin' spray, containing framycetin and gramicidin as antibacterial agents, was the most effective. With this spray, approximately 80% of nasal carriers were cleared in twenty-four hours (that is, by one application only), and 100% after two days' treatment.

The importance of deep nasal swabbing for detecting nasal carriers has been demonstrated.

We wish to thank the National Health and Medical Research Council, and the Hospitals and Charities Commission of Victoria for financial assistance. We are grateful to the Mother Rectress who kindly allowed these studies to be made in St. Vincent's Hospital. Roussel Laboratories, Imperial Chemical Industries of Australia and New Zealand, and Andrews Laboratories supplied the nasal preparations.

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SCARLET-FEVER-LIKE ILLNESS DUE TO STAPHYLOCOCCAL INFECTION

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AN illness resembling scarlet fever, but caused by *Staphylococcus pyogenes*, has been described on several occasions (Stevens 1927, Mackenzie 1934, Zinsser et al. 1939, Aranow and Wood 1942, Negro et al. 1956). We report three more cases.

Case-reports

Case 1.—A woman, aged 20, was admitted on Nov. 26, 1942, with the provisional diagnosis of scarlet fever. Six days before admission, she had a left axillary abscess; and, on the day of admission, a scarlatiniform rash appeared on the neck, trunk, and limbs. There was a history of measles, rubella, and pertussis in childhood, but of no other specific infections. The temperature was 102°F, pulse-rate 118. There was a large abscess in the left axilla. The fauces were mildly injected, but there was no exudate.

Investigations.—Culture of pus from the abscess gave a pure growth of *Staph. aureus*. The hæmolytic streptococcus was not isolated from repeated nose and throat swabs. The total white-cell count was 16,000, with a neutrophil leucocytosis.

Treatment.—The abscess was incised, and 20 ml. scarlatinal antitoxin was administered intramuscularly. A course of sulphanilamide, totalling 21 g., was given.

Progress.—The pyrexia subsided on the sixth day. The tongue peeled and the rash faded on the third day; thereafter, desquamation began, particularly on the palms and soles. When discharged on Dec. 17, the soles were still peeling.

Case 2.—A woman, aged 21, was admitted on Feb. 12, 1958, with a provisional diagnosis of septic abortion. Three days before admission, there had been vaginal blood-loss with diarrhœa and vomiting. Two days later, the patient aborted. A rash appeared on the trunk on the day of admission. There had been two normal pregnancies, but no previous miscarriages. The last menstrual period had been three months previously; the patient had suffered from nausea and vomiting, and had not felt really well during the pregnancy. There was a past history of measles only and there had been no contact with recent infectious disease.

The patient looked ill and toxic. There was a bright erythema on the trunk and limbs. The fauces and buccal mucosa were red, but there was no exudate. Several small cervical lymph-nodes were palpable. The blood-pressure was 100/70 mm. Hg. The size of the uterus corresponded to three months' pregnancy. Offensive placental fragments protruded through the os.

Investigations.—Culture of high vaginal and cervical swabs gave a pure growth of *Staph. pyogenes*, resistant to penicillin, but sensitive to chloramphenicol, streptomycin, the tetracyclines, and erythromycin. Culture of nose, throat, and post-nasal swabs also yielded a moderate growth of *Staph. pyogenes* with the same sensitivity. The urine contained a trace of albumin, pus cells, red cells, and granular casts, and coliform bacilli were grown on culture. Culture of the fæces was negative. Blood-culture was negative. The white-cell count was 12,000, with a neutrophil leucocytosis. The serum-potassium, serum-sodium, and serum chlorides were 3·2, 132, and 95 mEq. per litre respectively. The blood-urea was 115 mg. per 100 ml. The Wassermann reaction and the Kahn test were negative. *Treponema pallidum* was absent from three preparations from the mouth lesion. The gonococcal complement-fixation test was negative. The Dick test and the Schultz-Charlton test, done on admission, were both negative.

Treatment.—Fluids and electrolytes were administered by continuous intravenous drip. The patient was given crystalline penicillin, 500,000 units six-hourly, When the sensitivity reaction showed the organism to be penicillin-resistant, the drug was discontinued after 1·5 megaunits had been given, and tetracycline was administered orally, 750 mg. six-hourly, to a total of 10·5 g. An infection of the mouth due to *Candida albicans* then developed, and the tetracycline was discontinued. Nystatin, 250 mg. six-hourly, to a total of 5 g., together with local crystal violet effectively controlled this; but on Feb. 25, multiple furuncles appeared on the perineum and buttocks; and, five days later, on the right hand. Intramuscular streptomycin, 1 g. twice daily to a total of 13 g., was given, together with erythromycin, 250 mg. six-hourly, to a total of 6·5 g.

Progress.—Fever continued for twenty days, with temperatures up to 103°F. After a week, the blood-urea had fallen to 26 mg. per 100 ml., and the electrolytes were normal. The rash faded after three days and desquamation began on the seventh day, particularly on the hands, arms, and soles. When the patient was discharged on March 7, the uterus had involuted normally and the adnexa were clear. All the staphylococcal lesions had healed, apart from one boil on the thumb from which there was still a slight discharge.

Case 3.—A girl, aged 19, was admitted on April 28, 1959, with a provisional diagnosis of scarlet fever. Eleven days previously she had a boil in the right axilla; and two days before admission complained of headache, stiffness in the wrists and fingers, and sore heels. On the same day, a rash appeared on the hands, spreading to the legs and arms next day. There was a history of chickenpox and pertussis only in childhood. There had been no recent contact with infectious disease.

The patient looked toxic, had frank rigors, and was faintly jaundiced. The temperature was 103·6°F, pulse-rate 136, and blood-pressure 100/50 mm. Hg. There was a bright punctate erythema involving the trunk and limbs with definite folliculitis on the trunk. The fauces were red, the tonsils small and injected, but there was no exudate. The tongue was furred. Small lymph-nodes were palpable in the anterior triangles of the neck. There was a small, tense abscess in the right axilla. Both wrists were slightly swollen and hot, and there was some swelling of the proximal interphalangeal joints of the fingers of both hands.

Investigations.—The white-cell count was 26,800 (polymorphs 95%). Platelets 120,000 per c.mm. The erythrocyte-sedimentation rate (E.S.R.) was 45 mm. in the first hour (Westergren). In the corpuscle-fragility test, hæmolysis began at 0·44%, and was complete at 0·36%. The urine contained urobilin and urobilinogen in excess. The total serum-proteins were 6·1 g. per 100 ml. (albumin 3·6 g. per ml., globulin 2.5 g. per ml.). The direct van den Bergh test was positive. Total serum-bilirubin was 5·0 mg. per 100 ml. The liver-function tests were normal. Culture of pus from the abscess showed a heavy growth of *Staph. pyogenes*, phage-type 29. The hæmolytic streptococcus was not isolated from cultures of nose, throat or post-nasal swabs. Blood-culture was negative. The Dick test and the Schultz-Charlton test, done on admission, were both negative.

Treatment.—Crystalline penicillin, 500,000 units six-hourly, was given initially, but this was replaced by tetracycline, 750 mg. six-hourly orally, when the sensitivity pattern showed the staphylococcus to be penicillin-resistant.

Progress.—On the second day after admission, the patient was jaundiced and the rash was more pronounced. The axillary abscess ruptured spontaneously and discharged thick pus. The pyrexia abated on the fourth day, and the jaundice lessened. Peeling began on the palms and soles, and next day there was generalised desquamation. The joints were no longer swollen. By the tenth day, the desquamation was complete and the tongue was clean. The total serum-bilirubin was 0·5 mg. per 100 ml., and the direct van den Bergh test negative. The E.S.R. had fallen to 8 mm. The patient was discharged on the fourteenth day after admission, symptom-free. The axillary abscess had completely resolved.

Two months later, the patient was readmitted with a recurrence of axillary boils, but on this occasion there was no rash and no jaundice.

Investigation of the Staphylococcal Filtrate

A sterile filtrate was prepared from the staphylococcus isolated from case 1, and intradermal tests were done using (1) the filtrate alone, (2) the filtrate combined with scarlatinal antitoxin, and (3) the filtrate combined with staphylococcal antitoxin. The results of the tests were inconclusive.

A filtrate of the staphylococcal culture from the axillary abscess of case 3 was also prepared by the method described for the Dick toxin (Dick and Dick 1938). Dilutions of this filtrate, 1/10 to 1/10,000, were made, using a buffer solution. Intradermal tests on Dick-positive subjects, using these dilutions, were then carried out.

Our method of doing the intradermal test is to raise a button, approximately 5 mm. in diameter, at the site of injection. We have found by experience that injecting a fixed quantity of toxin does not mean that this amount will necessarily get into the tissues because there is usually leakage around the needle.

Dilutions of 1/100 gave a bright erythematous reaction, about 10 mm. in diameter, in susceptible patients. The reaction began four to six hours after injection and was maximal in twelve to eighteen hours.

After heating the filtrate to 100°C for sixty minutes, there was no reaction when it was injected intradermally into susceptible subjects. This preparation was used as a control in the subsequent experiments on 37 patients, chosen at random, suffering from diseases not associated with staphylococcal or streptococcal infection.

The staphylococcal filtrate (dilution 1/100) was injected intradermally into the anterior surface of the right forearm and the control into the left; the Dick toxin and control being administered vice-versa. An erythematous reaction measuring 5 mm. or more was regarded as positive, provided the control test was negative; or, where both were positive, the reaction to the toxin had to be appreciably larger than the control to be considered positive. The results are summarised in table I.

Of the 7 positive staphylococcal-toxin reactors, aged 2–5, 2 were Dick-negative; of the 9 in the group 6–15, 4 were Dick-negative. Both the patients in the over-15 group who were Dick-positive also reacted to the staphylococcal toxin.

TABLE I—REACTIONS TO DICK TOXIN AND TO STAPHYLOCOCCAL TOXIN (CASE 3) IN PATIENTS WITH DISEASES NOT ASSOCIATED WITH STAPHYLOCOCCAL INFECTION

Age (yr.)	Positive Dick reactors	Positive staphylococcal toxin reactors	Total
2–5	7	7	10
6–15	8	9	15
Over 15	2	6	12
Total	17	22	37

TABLE II—REACTIONS TO DICK TOXIN AND STAPHYLOCOCCAL TOXIN (CASE 3) IN 5 CASES OF SCARLET FEVER

Case	Sex	Age (yr.)	Day of disease	Staphylococcal filtrate (1/100)	Staphylococcal control	Dick toxin	Dick Control
1	M	5	2	Positive	Negative	Positive	Negative
			12	,,	,,	Negative	,,
2	F	4	2	,,	,,	Positive	,,
			8	,,	,,	Negative	,,
3	F	4	5	,,	,,	Positive	,,
			12	,,	,,	,,	,,
4	M	8	2	Negative	,,	,,	,,
			12	,,	,,	Negative	,,
5	F	6	3	Positive	,,	Positive	,,
			13	,,	,,	,,	,,

Similar intradermal tests were done on 5 consecutive cases of confirmed scarlet fever (all of whom had a heavy growth of β-hæmolytic streptococci in the throat swabs). These tests were done on admission and were repeated the day before discharge. The results are shown in table II.

These results suggested that the erythrogenic toxin elaborated by the staphylococcus was probably antigenically different from that produced by the β-hæmolytic streptococcus. This observation was confirmed to some extent by the fact that both the Dick and Schultz-Charlton tests were negative in cases 2 and 3 on admission, when one would have expected these tests to have been positive if the patient had scarlet fever.

Discussion

Certain strains of *Staph. pyogenes* can produce an erythrogenic toxin. Pilot and Afremow (1927) prepared a filtrate from a staphylococcal culture which gave an erythematous reaction measuring 2-5 cm. on intradermal injection. They found that antitoxin serum, prepared by injecting the filtrate into rabbits, neutralised the skin reaction, but that this serum had no effect on the erythrogenic toxin produced by the hæmolytic streptococcus. Stevens also noted in his cases that the rash was blanched by staphylococcal antitoxin, but was unaffected by the hæmolytic streptococcal antitoxin.

Satake (1927) isolated a hæmolytic *Staph. aureus* from the throat of a patient with scarlet fever, in whom search for the hæmolytic streptococcus had proved fruitless. He demonstrated an erythrogenic toxin in the filtrate from a culture of this staphylococcus, which produced a typical scarlet-fever syndrome when given in large doses to subjects whose skin reacted to the toxin.

Remé (1930) found that 12 out of the 15 strains of hæmolytic staphylococcus tested yielded an erythrogenic toxin. Mundt (1939) examined the filtrate from the cultures of 19 different strains of hæmolytic *Staph. aureus*, and found that 10 of these strains yielded an erythrogenic toxin which produced a reaction similar to the Dick test in Dick-positive subjects. She also showed that the addition of scarlatinal antitoxin neutralised the effect of this toxin. These findings were substantiated by Aranow and Wood (1942) who isolated a *Staph. aureus* from repeated blood-cultures of a patient with osteomyelitis in whom severe scarlatiniform eruption developed.

In two of our patients (cases 2 and 3), where the Schultz-Charlton test was done on admission, there was no blanching of the rash when scarlatinal antitoxin was injected intradermally.

Toxicity, a bright erythema, and profound desquamation were features of our three patients. The jaundice in case 3 was undoubtedly caused by intravascular hæmolysis due to the severity of the infection. It is surprising that the staphylococcus was not isolated from the blood-culture in this case, but only one culture was possible before starting antibiotic therapy.

Summary

In three illnesses resembling severe scarlet fever the only pathogen found was the *Staph. pyogenes*. It was demonstrated, by intradermal tests on susceptible subjects, that the filtrate, prepared from the culture of the staphylococcus isolated from case 3, contained an erythrogenic factor. This erythrogenic toxin may differ in its antigenic properties from that produced by the hæmolytic streptococcus.

We should like to thank Dr. William Gunn and Dr. A. M. Ramsay for their encouragement and for access to the records of case 1 which was not seen by either of us. We are also indebted to Dr. R. E. O. Williams, Staphylococcal Reference Laboratory, Colindale, for phage-typing the organism isolated from case 3. It is a pleasure to acknowledge our gratitude to Miss M. E. Beacock, librarian of the Royal Free Hospital.

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RAPID DESTRUCTION OF ANTITETANUS SERUM IN A PATIENT PREVIOUSLY SENSITISED TO HORSE SERUM

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PARENTERAL administration of foreign serum stimulates the formation of precipitating antibodies and may sensitise the recipient, so that a subsequent dose of serum produces anaphylactic reactions. Glenny and Hopkins (1922) showed that in laboratory animals a second dose of foreign serum disappears from the blood much more rapidly, and that, if this serum contains antibodies, these remain in the circulation for a very much shorter time. The duration of passive immunity conferred by antitetanus serum is believed to be likewise reduced in patients who have previously received tetanus antitoxin (Payling Wright 1958).

We report here a case in which hypersensitivity to horse serum developed as the result of antitoxin therapy. Circulating tetanus antitoxin and antibodies to horse serum were estimated. The rapid fall in circulating antitoxin and the rise in titre of antibodies to antitoxin support Payling Wright's view.

Case-record

A leatherworker, aged 20, sustained a compound fracture of the right tibia and fibula in a motor-cycle accident on Dec. 5, 1958. He was given 1500 units of antitetanus serum intramuscularly, and was admitted to King's College Hospital under the care of Mr. R. C. F. Catterall. A few hours later the compound fracture was explored, a skin graft applied, and the limb externally fixed. 1 million units of crystalline penicillin was

given intramuscularly every twelve hours for four weeks, during which time further skin grafts were applied. The area of the wound was subsequently reduced to about 1 sq. cm. over the tibia anteriorly. The patient was discharged from hospital in an above-knee plaster on Feb. 25, 1959. On June 2, 1959, discharge from the wound was very slight and the patient was bearing weight on his leg without pain.

On June 16, 1959, he noticed that his back was stiff and he had difficulty in moving his jaw. Two days later spasms had spread to his back and abdominal muscles. Tetanus was diagnosed, and he was admitted to hospital under the care of the late Dr. A. Gilpin.

Treatment

Because of the patient's previous serum injections, test doses of antitetanus serum were given subcutaneously: 0·2 ml. (1000 units) and, after an interval of forty-five minutes, 1 ml. (5000 units). No systemic reactions were observed, but both doses gave rise to local erythema 2 cm. in diameter. He was therefore given 100 mg. of chlorpromazine intramuscularly, and a further 10 ml. of antiserum was injected very slowly intravenously. After 6 ml. had been injected, he became breathless and complained of pricking in the face. Tetanic spasm involved the back and limbs. 3 ml. of a 1 in 1000 solution of adrenaline was given intramuscularly and subcutaneously over the next five minutes. He became shocked, and his blood-pressure fell to 60/0 mm. Hg. Because of the severe reaction, and the likelihood that the condition was chronic tetanus, no further antitetanus serum was given. The patient's condition deteriorated over the next few days; spasms occurred at irregular intervals. Chlorpromazine and pethidine were given for sedation and to alleviate the pain of the sustained muscular contraction. A wound-swab grew *Clostridium tetani*. The wound was thoroughly cleansed; extensive debridement was not attempted as this would have necessitated amputation. By June 28, 1959, two weeks after his first symptoms, the patient's condition had begun to improve; the stiffness eased, and a month later he was discharged from hospital after receiving the first dose of a full course of tetanus toxoid without ill effect.

Investigations and Discussion

Serum was taken from the patient on the sixth, ninth, and fourteenth days and six months after the last injection of antiserum, and its tetanus-antitoxin content was titrated in mice by the method of Glenny and Stevens (1938). The normal antitoxin values to be expected after an injection of 30,000 units of antitoxin have been estimated from data given by Barr and Sachs (1955). These values are compared with the patient's in table I. The level in the patient on the sixth day is half of that expected, and all effective immunity has disappeared by the ninth day. This destruction is not quite as rapid as that in animals (Glenny and Hopkins 1922), in which by the fourth day no antitoxin was detectable.

TABLE I—OBSERVED AND EXPECTED SERUM ANTITOXIN LEVELS AFTER INJECTION OF 30,000 I.U.

Days after injection	Observed values (antitoxin units per ml.)	Expected values (antitoxin units per ml.)
6	1·2	2·4
9	<0·01	1·6
14	<0·01	1·0

Antibody to horse serum and to equine tetanus-antitoxin globulins was titrated by an agar-gel precipitation method, and by hæmagglutination of sensitised tanned cells. The results (table II) show that the sera taken on the ninth and fourteenth days, which contained negligible amounts of antitoxin, have high titres of antibody to horse-serum proteins. These antibodies were still detectable after six months.

Serum taken on the fourteenth day was also tested against normal sheep, pig, and goat serum, as it has been suggested that antitoxin prepared in other animals might be used for patients sensitive to horse serum.

TABLE II—TITRATION OF ANTIBODY TO HORSE SERUM AND TO TETANUS ANTITOXIN

Days after injection	Titration method			
	Agar-gel precipitation		Hæmagglutination	
	Normal horse serum	Tetanus antitoxin*	Horse serum	Tetanus antitoxin*
6	1/8	1/8	1/25	1/25
9	1/128	1/128	1/625	1/625
14	1/128	1/128	1/625	1/625
180	0	0	1/25	1/5

* Wellcome brand, consisting of enzyme-refined horse globulins, was used.

Sera from all three species gave positive precipitation reactions with the patient's undiluted serum and hæmagglutination to a titre of 1/25. Though these reactions were very much weaker than those found with horse serum, the cross-reactions suggest that foreign serum should be administered with care to patients sensitive to horse serum.

Summary and Conclusions

Tetanus developed in a patient who was hypersensitive to horse serum.

Tetanus antitoxin in the patient's serum was estimated shortly after a dose of 36,000 units of antitetanus serum. Six days later 1·2 units per ml. (half the expected value) was found, and on the fourteenth day no antitoxin was detectable. Precipitating antibodies to horse-serum globulins were found at a higher titre in the fourteenth-day than in the sixth-day sample and were still present, though at low titre, six months later.

This case illustrates the following points:

1. The protection given by tetanus antitoxin is greatly reduced in patients with anaphylactic reactions and may also be reduced in those who, though not obviously hypersensitive, have received horse serum before.

2. Because of cross-reactions, tetanus antitoxin from animals other than the horse is unlikely to be of practical use in the treatment of those hypersensitive to horse serum.

3. The most effective means of reducing the incidence of hypersensitivity reactions and their sequelæ is active immunisation, particularly of those who have received prophylactic antiserum. Indeed, if this patient had been actively immunised soon after the accident he might possibly not have had tetanus.

We wish to acknowledge our indebtedness to Mr. R. C. F. Catterall and the late Dr. A. Gilpin for permission to publish; to Miss M. Barr, of the Wellcome Research Laboratories, for the estimations of antitoxin; to Dr. Leslie Cole for advice on treatment of the patient; and to Sister O. Bonner and her staff for their expert nursing.

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"... a cry was soon echoing from committee to committee: 'The smaller the school the better the school' (a fore-runner perhaps to one of Parkinson's Laws). Now, it must be obvious to everyone that large classes are bad, but is the reverse true? Are small classes necessarily good? The answer is, no. Once the numbers drop below a certain critical point they are definitely bad. Every clinical teacher knows that the success of ward-round teaching depends on the presence of a *group* of students. A worth-while discussion then ensues, one man is set against another, diverse opinions are expressed, and slowly the essential facts and truths are cleared of their irrelevancies. How different and dreary are ward rounds with one solitary student! And how little real teaching does he get!"—Prof. J. CHASSAR MOIR. The Future of the Clinical School at Oxford: a Symposium. *Oxford Medical School Gazette*, 1960, **12**, 95.

Reviews of Books

Calcium Metabolism and the Bone

PAUL FOURMAN, M.D., D.SC., F.R.C.P., senior lecturer in medicine, Welsh National School of Medicine. Oxford: Blackwell Scientific Publications. 1960. Pp. 325. 37*s*. 6*d*.

CALCIUM metabolism has been attracting more and more attention since the appearance of a celebrated American monograph in 1948. Recent international meetings have revealed worldwide interest in such matters as the problem of fractures in the elderly, the early diagnosis of primary hyperparathyroidism, the biological half-life of bone-seeking isotopes, and the nutritional requirements for calcium and vitamin D. All clinicians and other interested workers have, however, been aware of the need for an additional textbook. Dr. Fourman's distinguished work is therefore very welcome, and it deserves to be widely read. He reviews the whole subject in matter-of-fact manner, steering a fair course between dogmatism and excessive caution. 74 pages of references testify to his hard work and well-selected reading and will be invaluable to many workers in all branches of calcium metabolism. Students and general clinicians, on the other hand, will be more impressed by the conciseness of the writing and the skilful balance which has been preserved between biochemical and clinical aspects. There are very few illustrations, but that has kept down the cost, and the book can certainly be recommended as very good value for money.

Epilepsy and Related Disorders

W. G. LENNOX, M.D., SC.D., associate professor of neurology emeritus, Harvard University School of Medicine; M. A. LENNOX, M.D., member, Institute of Neurophysiology, Copenhagen. London: J. & A. Churchill. 1960. Pp. 574 (vol. I). 594 (vol. II). 96*s*.

Dr. W. G. Lennox spent a busy life studying the problems of epilepsy, and he acquired a vast experience of the many variations of the disease. Written in conjunction with his daughter, this two-volume work brings together this knowledge and represents the clinical practice of a devoted doctor who was an enthusiastic pioneer for the welfare of epileptics. He was eager to accept all the help science could give: and he himself contributed both to detailed scientific applications in diagnosis and treatment and to the diffusion of a more rational and scientific attitude to the subject. But he was also willing to be moved by the human problems of epilepsy, and this lent energy and enthusiasm to his endeavours especially in therapy and management. For many years, as head of the seizure division of the Boston Children's Centre, he guided the approach in this subject both of this hospital and of American pædiatrics in general. All this is woven into the book, which presents the modern view of epilepsy for which Lennox was largely responsible.

The first volume is concerned mainly with clinical description, the second rather more with detailed diagnosis and treatment: the last chapter of the first volume, on genetics and the broad factors of causation, bridges the gap. A useful list of references both to books and papers on the subject is appended.

Although this is a full and comprehensive account of epilepsy and will be an essential source of reference to neurologists for many years to come, it remains in style and emphasis the personal testament of a doctor: no bad thing perhaps at a time when science often seems temporarily to be in competition rather than collaboration with humanism in medicine.

Chemicals in Food and in Farm Produce: Their Harmful Effects

FRANKLIN BICKNELL, D.M., consulting physician to the French Hospital, London. London: Faber & Faber. 1960. Pp. 180. 12*s*. 6*d*.

THE many substances now being added to our food have become a nightmare to legislators and to other people who have thought about this subject during the past fifteen years, and this book gives an interesting account of some of the additions. The first chapter (on naturally occurring poisons) and the last (on the dangers of insecticides and similar substances to worms, fish, and insects) are perhaps the best. The author is a firm believer that food, the whole food, and nothing but the food, is the only safe and proper thing to eat. Flour must be unbleached, fats not hydrogenated, colouring-matter and emulsifying agents strongly discouraged. So far so good, but here and there he has overstated his case. How true is it, for instance, that toxic substances added to our food explain many of our recognised congenital abnormalities? Fluoride is one of the few additions to food which Dr. Bicknell judges worthy of consideration.

There are advantages as well as disadvantages in processing foods for a civilised community, and many people think that our scientists, industrialists, and legislators have not done all that badly by most of our foods—so far at any rate.

This is a good and well-documented book. It can be recommended to objective readers who are not likely to be frightened by the possibility of finding "death in the pot".

The Collected Papers of Paul Ehrlich

Compiled and edited by F. HIMMELWEIT, M.D., PH.D., F.R.C.P.E., director, department of virus research, Wright-Fleming Institute, St. Mary's Hospital Medical School, London. With the assistance of the late MARTHA MARGUARDT. London: Pergamon Press. 1960. Vol. 2. Pp. 562. Vol. 3. Pp. 615. £8 each.

THERE were three main phases in Ehrlich's career, and if his published works be arranged according to their subject they are found to be in approximately chronological order. His graduation thesis was upon staining methods using the aniline dyes which had become available for the first time a few years before; and these same dyes, used as chemical reagents, occupied him until 1891. Then the discovery of antitoxins by von Behring and Kitasato turned his attention to immunology (and later to the immune phenomena provoked by certain transplantable tumours). By 1904 techniques had been described, notably by Laveran and Mesnil, for the maintenance of strains of some parasites in laboratory animals, and Ehrlich resumed his work with dyes. But he was now concerned with their action in experimental trypanosomiasis and spirillosis. These were the studies which led, in 1909, to salvarsan, and which continued until his death, six years later, at the age of 61.

These two volumes of the series cover the second and third of these periods. One contains just over fifty articles on immunotherapy and immune reactions, and it includes the classic monograph on the assay of diphtheria antitoxin which was written in the establishment created by the State for Ehrlich to head, the Royal Prussian Institute for Serum-testing (housed partly in a stable, partly in a converted bakery). The other volume has a similar number of papers on chemotherapy, beginning with his first venture, when he demonstrated the action of methylene-blue in malaria. Ehrlich was the son of a Silesian innkeeper, and the article concludes with a delightful, but almost irrelevant, note upon a little known physiological property of newly brewed beer.

These books are beautifully bound and printed; because the original text has been used throughout, most of the contents are in German. Translations are appended, however, to some of the most famous papers.

Equipment for the Disabled

Compiled by MARGARET AGERHOLM, M.B., lecturer, ELIZABETH M. HOLLINGS, M.A.O.T., head occupational therapist, WANDA M. WILLIAMS, M.A.O.T., warden, Mary Marlborough Lodge, Nuffield Orthopædic Centre, Oxford. London: National Fund for Research into Poliomyelitis and Other Crippling Diseases. 1960. 4 vols. 120*s*.

MANY patients and many institutions have developed special skills and devices to cope with almost every aspect of an incapacity. Unfortunately there is no clearing-house for collating information on their methods, or for making it available to a wider circle. The council of the Poliomyelitis Research Fund have gone a long way towards remedying this by publishing this "index".

Each volume is a stout folder, containing a number of loose-leaves in an "open-flat" type of steel clip. These pages are indexed under such headings as Transport, Cooking, and Personal Toilet. Each item has a separate page, with an illustration and an address from which it is obtainable. The equipment is of three varieties: specially manufactured; purchasable in ordinary shops, but with a particular value for the disabled (for example, an electric iron which weighs only 2 lb.); and home-made (such as devices for turning keys or door-handles).

The index, sold on a non-profit basis, is to be supplemented by further pages issued to purchasers from time to time. It should be available in every hospital.

Urology in General Practice

IAN PARTON, M.B., B.SC., F.R.C.S., assistant urologist, Auckland Hospital, New Zealand. London: Butterworths. 1960. Pp. 293. 45*s*.

DESIGNED for the general practitioner as a guide to procedure in urological disease and emergency, this book abounds in good humour and common sense and gives a brief survey of current urological practice without going too far into the realms of academic controversy. From it the practitioner will gain a shrewd idea of the significant combinations of symptoms and signs in genitourinary disorders, and the indications for seeking specialist advice. This advice may vary according to the available means for diagnosis and treatment, and also the inclination and ability of the practitioner to perform minor surgery. Conditions in New Zealand clearly differ from those in urban areas of Britain: access to a urological centre may be more difficult so that there is greater scope for the practitioner to make diagnostic decisions and to undertake emergency treatment. Nevertheless the practical information in this little book will be of interest to all as a thoroughly sensible review.

Disc Lesions and Other Intervertebral Derangements

E. J. CRISP, M.D., D.PHYS.MED., consultant physician emeritus in physical medicine, Guy's Hospital, London. Edinburgh: E. & S. Livingstone. 1960. Pp. 158. 15*s*.

IT is a Shavian parodox that doctors write most on those diseases about which they know least. Certainly the number of books and articles they continue to produce on such topics as spinal arthritis, postural defects, and disc protrusions indicates the problem posed by the multitude of patients seeking relief from backache and sciatica.

Dr. Crisp makes no claim to have solved this problem. His book is not prefaced (as many are) with a lengthy and hypothetical discussion on the ætiology of backache. He is concerned only with the practical management of some half-dozen clearly defined syndromes associated with pain in the back. Manipulation and traction, the mainstays of his method, are described in detail, but manipulation is not extolled as a universal panacea, and traction is not applied, Procrustean fashion, to every patient. An interesting use is made of strapping, to relieve the discomfort of an acute disc prolapse, and he attributes the beneficial effects of the old-fashioned belladonna plaster, not to its medicinal properties, but to the skin tension and restriction of movement it produced.

In recent years the treatment of back pain has become increasingly conservative, and this is a very useful primer on nonoperative measures. From later editions one would like to learn the author's views on the place—if any—of sedatives, relaxants, and other drugs.

Disease and the Advancement of Basic Science

Editor: HENRY K. BEECHER. Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1960. Pp. 416. 100*s*.

WHAT is the best understood of all diseases? It is disconcerting to learn of Dr. Alex Bearn, of the Rockefeller Institute, that it is one of which many doctors know little. Yet, as he points out, sickle-cell anæmia and the related hæmoglobinæmias are the only diseases of which we can be said to have a "molecular knowledge". (The abnormality is an inherited anomaly of the hæmoglobin molecule: in the reduced form the molecules cohere, to produce needle-like crystals which are longer than the diameter of the red cells, and so deform them.) The chemical and physical data yielded by the investigation of such diseases are important contributions to non-clinical sciences. The same is true of the endocrine disorders, which are commonly the first diseases a medical student studies. He sees in them a demonstration of the part physiology has played in the advancement of medicine: yet they are, in fact, outstanding examples of a converse relationship by which the study of a pathological process has cast light upon normal function.

This symposium is concerned with just this relationship of medicine to the ancillary sciences. Only three of its twenty-one chapters, however, deal with hæmatology and the ductless glands. The others examine the results of research into (among other conditions) virus infections, rheumatism, and deafness. All are written in masterly fashion by acknowledged experts, but that by Dr. Percival Bailey is particularly fascinating, for he reviews the steps by which our understanding of neurophysiology has advanced. These come from observations as far apart as those of Hippocrates when a psychotic patient developed malaria, and of Hoffmann when he was accidentally poisoned with lysergic acid.

Medical Electronics (*Proceedings of the Second International Conference on Medical Electronics, Paris, 1959*. London: Iliffe. 1960. Pp. 614. £7 5*s*.).—Edited by Dr. C. N. Smyth, this book records a conference that attempted "to unite the disciplines of medicine and electrical engineering". 80 papers are given in full, with the subsequent discussions, and some 60 others in abstract. Most of the papers are in English but some are in French. Many of the abstracts are rather too short, and some of the papers are on subjects little connected with electronics, though interesting in themselves. There remain many able contributions describing the design, construction, and application of scientific instruments for the collection of physiological data in human or animal subjects. A useful introductory section on electrophysiological techniques includes excellent papers on muscle potential amplifiers (L. H. Montgomery and Sam E. Stephenson) and on eye-movement recording (by several British authors). The book should find a place in every medical library, for it contains an abundance of practical information not conveniently available elsewhere. Regrettably, much of the enterprise and ingenuity revealed here will never be fully exploited. Clinicians generally prefer less spectacular methods of investigation, and on the whole they are right. What is needed is for first-class physicists and electrical engineers to join teams of doctors in basic research, resisting the temptation to dissipate energy in producing more instruments or gadgets. The International Federation for Medical Electronics would do well to organise smaller meetings for the study of more fundamental problems at a higher intellectual level. Further gatherings of back-room boys may be useful but will not be decisive.

The Electrical Activity of the Nervous System (2nd ed. London: Pitman Medical Publishing Co. 1960. Pp. 273. 35*s*.).—The new edition of Dr. Mary Brazier's book remains a valuable source of reference to classical work on the electrical activity of the nervous system. For the neurologist it outlines clearly and succinctly the electrophysiological background of clinical phenomena in the nervous system. Although clinical practice must always have a discipline and frame of reference of its own, it must also take cognisance of established physiological facts, and neurology is entering once more a phase in which clinical problems in nerve and muscle function must be increasingly interpreted in terms of disordered physiology. Dr. Brazier's book is a useful guide to established fact and worthwhile hypothesis. It also fulfils another and increasingly important function in bridging the gap betweeen the findings of experimental and laboratory neurophysiology and those of clinical experience. It can be recommended as an up-to-date and balanced guide both for the final-year physiology student and the clinician who wishes to begin or renew his acquaintance with the electrical activity of the nervous system.

THE LANCET

LONDON 3 DECEMBER 1960

Myocardial Infarction

THE natural history of coronary occlusion and myocardial infarction has become even more important now that anticoagulant drugs have been accepted as standard treatment in the acute phase and are commonly used in the long-term prophylaxis of further attacks. Two studies have largely confirmed earlier reports about the prognostic factors influencing the outcome of the acute attack, and illustrate how selection of cases affects the mortality-rate. BEARD et al.[1] studied 503 U.S. veterans, all suffering from an initial myocardial infarction confirmed by an electrocardiogram. Since these workers were particularly interested in the younger age-groups all records of those under 50 years were included, but only a sample of available patients over that age were studied; thus 36% of patients were under 50, and the mortality in the first two months for the whole series was 15%. By contrast WHITE et al.[2] found a mortality in the first six weeks of 61% among 344 unselected male patients, of whom 70% were over 60 years of age and 28% had had a previous infarction. In both series the mortality rose considerably with advancing age—in the series of BEARD et al., in those over 60 the mortality was more than double that in those under 60. Plainly the different age-distribution accounts for much of the disparity between the two series and BEARD et al.'s series is also likely to have contained a lower proportion of patients who died shortly after admission. In both groups severe shock or congestive failure more than trebled the immediate mortality, and WHITE et al. found that shock was a particularly bad sign in patients with a previous infarct. High fever for more than a few days, a leucocytosis above 15,000 per c.mm., and any cardiac arrhythmia were all associated with a higher immediate mortality. BEARD et al. report a mortality of more than twice the overall rate in cases where thromboembolic complications developed, but do not state whether death was usually due to pulmonary embolism. In both series hypertensive patients had a higher mortality in the acute attack; BEARD et al. found a significantly worse prognosis in patients with angina for longer than a month before infarction, while WHITE et al. were particularly impressed by the high mortality in young diabetics. Generally speaking, bad prognostic signs are those indicating a large area of infarction.

Whereas the immediate mortality-rates vary widely, the five-year-survival figures, as BEARD et al. point out, agree remarkably closely. This is emphasised by MCMICHAEL and PARRY[3] in a critical analysis of the factors influencing the long-term prognosis after coronary-artery occlusion. Their review of the numerous published series [1 4–18] suggests that about 65% of survivors of the acute attack will be alive after five years, but the prospect declines with increasing age, so that those series [11 16] containing a higher proportion of old patients have a correspondingly diminished five-year-survival rate. Certain features of the acute illness not only worsen the immediate prognosis but also militate against long-term survival. Especially notable among these are congestive failure, cardiac enlargement, arrhythmias, previous infarction, and diabetes: chances of survival for five years are roughly halved in those with cardiac failure.[9 12–15] Other factors, such as economic class and ability to take extra care of the health, may contribute to a survival-rate above the average. MCMICHAEL and PARRY therefore conclude that the slightest degree of unintentional bias in the selection of patients for long-term anticoagulant treatment and control groups could profoundly influence the results, particularly if the numbers are small. They suggest that such bias may in fact have vitiated results, since in three large trials [19–21] the survival-rates of the control groups were rather below the lower limit expected in a group of untreated patients, whilst in another trial [22] heart-failure was twice as common in the control group as in the treated group. Furthermore, no treated group has yet had a survival-rate above the upper limit of the range expected in untreated cases—though admittedly most results are slightly better than the average.

MCMICHAEL and PARRY suggest that the only benefit apparent from long-term administration of anticoagulants in the two most careful studies yet reported—those of BJERKELUND[20] and the Medical Research Council[23]—is a slightly lower mortality-rate in the first few months after infarction. BJERKELUND found this only in men under 60, and the difference was also less notable in older men in the Medical Research Council trial. In neither series did women benefit at all. Reported trials have invariably stressed the reduced incidence of recurrent infarction in treated patients; but recurrent infarction is often difficult to diagnose, and sudden death after previous infarction is not always

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8. Weiss, M. M. *Amer. J. med. Sci.* 1956, **231**, 9.
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18. Richards, D. W., Bland, E. F., White, P. D. *J. chron. Dis.* 1956, **4**, 415.
19. Nichol, E. S., Keyes, I. N., Borg, J. F., Coogan, T. J., Boehrer, T. J., Mullins, W. L., Scott, T., Page, R., Griffith, G. C., Massie, E. *Amer. Heart J.* 1958, **55**, 142.
20. Bjerkelund, C. J. *Acta med. scand.* 1957, **158**, suppl. 330.
21. Suzman, M. M. Personal communication to McMichael and Parry (footnote 3).
22. Manchester, B. *Arch. intern. Med.* 1957, **100**, 959.
23. Report of the Working Party on Anticoagulant Therapy in Coronary Thrombosis to the Medical Research Council. *Brit. med. J.* 1959, **i**, 83.

due to this cause. In any series where sudden death from other causes is not clearly excluded, the incidence of recurrent infarction is liable to be overestimated; and this criticism may apply to the M.R.C. trial. In addition there is disagreement as to the duration of protection: BJERKELUND found no difference in his two groups after one year nor at any time among those over 60, whereas the M.R.C. trial suggests that protection continues into the second year.

MCMICHAEL and PARRY's analysis has made them critical of the claims advanced for long-term anticoagulant therapy, particularly as a means of prolonging survival or preventing recurrence. FLOREY [24] has remarked that the assumption that an anticoagulant will prevent thrombus formation is not necessarily correct: cardiac infarction has been reported in hæmophiliacs [25 26] and GILCHRIST and TULLOCH [27] found no real difference between the incidence of mural thrombi in patients who were receiving anticoagulants and those who were not. If anticoagulant drugs prevent arterial thrombosis, why should their prophylactic action apparently be confined to the first few months after infarction? MCMICHAEL and PARRY suggest that either their effect may be in some way related to the healing phase of infarction, or sudden cessation of treatment in controls renders them unduly prone to further infarction.

The acid tests of any form of treatment are whether it is effective and whether it is safe: MCMICHAEL and PARRY are clearly unconvinced, and they remark that fatal hæmorrhage can result from the use of anticoagulants. If their arguments are accepted—and correspondence has already shown that their reservations are shared by others—then our earlier estimation of long-term anticoagulant treatment [28] was overhopeful and it would seem logical to discontinue anticoagulant therapy after six months or a year, as BJERKELUND originally recommended.

The Biology of Metastasis

AMONG the more perplexing current biological problems are those concerned with cell "recognition" and cell differentiation. Up to what level can cells, as distinct from the whole animal, discriminate between "self" and "not self"? Have cells the inherent mechanisms to develop into organs and tissues, without outside "information"?

In 1908 WILSON [29] noted that when sponges were squeezed through a fine silk mesh, individual sponge cells were liberated. Left in a dish of sea-water, the individual cells moved over the surface of the dish, came into fresh contact with each other, and reaggregated to form new sponges. HOLTFRETER [30] found that amphibian embryos could be dissociated into single cells by briefly raising the pH of their environment to about 9·7. This treatment did not interfere with the viability of the isolated cells or with their subsequent differentiation, when their environment was brought back to physiological pH8. When mixtures of different types of cells, dispersed from the same embryo, were cultured, it was clear that, although initially any of the cells might unite indiscriminately with any other cells, they eventually sorted themselves out so that aggregates of like cells were formed. HOLTFRETER concluded that the sorting-out processes were largely due to positive or negative affinities of the cells: that is to say, in the reaggregation process cells of the same tissue (homotypic) making contact with each other would cohere permanently, whereas cells from unlike tissues (heterotypic) would not.

In 1952 MOSCONA [31] described the reaggregation of cells from chick embryonic organs which had been dispersed by the action of trypsin. He found that aggregates formed in suspensions of chondrogenic cells gave rise to nodules of cartilage; suspensions of isolated mesonephric cells produced aggregates which developed into vesicular and tubular structures resembling the excretory tissue of the embryo. Later MOSCONA showed that, when suspensions of chondrogenic and myogenic cells were cultured together, aggregates were formed in which the cells sorted themselves out so that an inner nodule of cartilage was differentiated, and this was surrounded by an envelope of myogenic cells. In 1957 MOSCONA [32] described tissue specificity in the reaggregation patterns of trypsin-dispersed chondrogenic, nephrogenic, and hepatogenic cells from the embryonic mouse. Cells from like organs aggregated together. Furthermore, when mixed cell-suspensions from 12-day-mouse and 4-day-chick embryos were cultured, chimæric (organ) aggregates were formed provided that the cells from the two species came from the same type of tissue. Cells from different tissues, even when obtained from the same embryo, did not form stable heterotypic aggregates. In this type of experiment, therefore, tissue-specificity took precedence over species-specificity. Lately P. WEISS and A. C. TAYLOR [33] have shown that organs from 8–14-day-old chick embryos, which have been disaggregated with mixtures of trypsin and papain, re-form and undergo a remarkable degree of development when cultured on the chorioallantoic membranes of 8-day-old embryos. After 9 days' culture on chorioallantoic membranes, grafts of completely disorganised metanephric cells form symmetrical organs with clearly defined cortices, medullæ, tubules, and malpighian corpuscles.

The experimental evidence shows that, in the sorting-out processes that occur in cell suspensions, the capabilities of cells for differentiation and specialised recombination are associated with information on the cell surface which makes recognition at cell level possible. L. WEISS [34] has suggested that this recognition may be expressed in terms of cell adhesion. TYLER,[35 36] P. WEISS,[37 38] and SPIEGEL [39] suggested that cellular

24. Florey, H. *ibid.* 1960, ii, 1329.
25. Borchgrevink, C. F. *Lancet*, 1959, i, 1229.
26. Stewart, J. W., Acheson, E. D. *ibid.* 1957, i, 1121.
27. Gilchrist, A. R., Tulloch, J. A. *Scot. med. J.* 1956, **1**, 1.
28. *Lancet*, 1958, i, 417.
29. Wilson, H. V. *J. exp. Zool.* 1908, **5**, 245.
30. See Townes, P. L., Holtfreter, J. *ibid.* 1955, **128**, 53.
31. Moscona, A. *Exp. Cell. Res.* 1952, **3**, 535.
32. Moscona, A. *Proc. nat. Acad. Sci., Wash.* 1957, **43**, 184.
33. Weiss, P., Taylor, A. C. *ibid.* 1960, **46**, 1177.
34. Weiss, L. *Int. Rev. Cytol.* 1960, **9**, 187.
35. Tyler, A. *Proc. nat. Acad. Sci., Wash.* 1940, **26**, 249.
36. Tyler, A. *ibid.* 1946, **32**, 195.
37. Weiss, P. *Growth*, 1941, **5**, suppl. p. 163.
38. Weiss, P. *Quart. Rev. Biol.* 1950, **25**, 177.
39. Spiegel, M. *Biol. Bull.* 1954, **107**, 149.

adhesion invokes mechanisms similar to antigen-antibody reactions, and that differences in cell adhesiveness may reflect antigenic change. It is therefore interesting that WEILER [40 41] has demonstrated antigenic differences between normal rat liver cells and those from butter-yellow hepatomas. It might be expected that there would be different contact reactions between normal cells on the one hand, and between normal and malignant cells on the other.

The work of ABERCROMBIE et al.[42] has revealed that when sheets of normal embryonic fibroblasts in culture come into contact with each other, either the cells move away from each other or, if this is not possible, migratory movements stop altogether; this feature has been termed " contact inhibition ". On the other hand, when various types of malignant cells come into contact with normal fibroblasts under the same experimental conditions, the malignant cells move through and over sheets of the normal cells. As ABERCROMBIE et al.[42] pointed out, it would be rash to directly relate in-vitro experiments with embryonic tissue to the observed invasive behaviour of human tumours in vivo. Nevertheless, invasion of normal tissues by malignant cells may be related to surface changes that make the malignant cells less adherent to themselves and other cells, and thus more mobile than normal cells. Moreover, COMAN's work [43 44] suggests that the constituent cells of some tumours are less sticky for each other than the constituent cells of normal organs. If the observations of ABERCROMBIE and COMAN apply generally, then invasion and metastasis can be regarded as deficiencies in the adhesiveness of tumour cells. Thus the problem is defined rather than explained, since pathetically little is known about the biophysical bases of adhesion.

When the reasons for lack of adhesion are sought, three main factors must be considered. These are the tumour-cell surface, the surface to which it sticks, and the microenvironment at the cell surface. The study of each of these three factors is extremely difficult. It is not agreed what constitutes the cell surface, since extraneous materials may or may not be regarded as an integral part of the cell. On electronmicrographic evidence it seems likely that the plasma membranes of adherent cells are invariably separated by about 200Å; thus in a sense cells can be regarded as sticking to intercellular or intermembranous material. Is this material the key to invasion and metastasis? The microenvironment at cell surfaces is probably quite different from the enveloping tissue-fluids, owing to physicochemical influences, and may vary at different parts of the cell surface owing to microheterogeneities. All or any one of these factors could bring about changes in adhesive potential.

As more knowledge is obtained about factors affecting cell surfaces and contact, it may conceivably become possible to influence these therapeutically. In this event, it might prove feasible to control invasion and metastasis of malignant disease, leaving the field open for safe surgical removal of primary growths.

40. Weiler, E. *Z. Naturf.* 1952, **7**, 324.
41. Weiler, E. *ibid.* 1956, **11B**, 31.
42. Abercrombie, M., Heaysman, J. E. M., Karthauser, H. M. *Exp. Cell Res.* 1957, **13**, 276.
43. Coman, D. R. *Cancer Res.* 1944, **4**, 625.
44. Coman, D. R. *ibid.* 1953, **13**, 397.

Hospital Infection

AT the end of October WILLIAMS, BLOWERS, GARROD, and SHOOTER[1] produced a book of great importance on hospital infection. No better single source of information on this subject is to be found anywhere, and a corresponding welcome is assured. It is because of this, and because of the excellence and authority of the work, that we look at its contents with special care. Of the three challenges it offers, the first is the challenge of the knowledge that our hospitals are doing harm to some of the sick within their walls. The second and third are put by the authors in their preface:

" We anticipate criticism of the text on two grounds. It may be said that too much space is devoted to staphylococcal infection, perhaps because the authors have themselves made a special study of it. . . . Secondly, we may be accused of too agnostic an attitude because we have expressed firm conclusions only when the evidence seems fully to justify them."

To examine these challenges separately may be as good an approach as any to the task of describing and commenting on a book which deserves and requires to be read by clinicians, matrons, nurses, administrators, laboratory workers, and general practitioners.

First, the challenge of the subject itself. Some deprecate reiteration of appeals[2] because, by a few simple and obviously necessary steps, they have reduced the infection-rate in clean surgical wounds to a very low level; and it is encouraging to know that this can be done. Simply for a surgical chief to say to all the members of his unit that wound sepsis is a most important problem which he wishes to be fully and frankly assessed, discussed, and unemotionally dealt with will of itself often work a transformation. If action includes the recording of all infections and (still better) the ascertainment week by week of the infection-rate and its discussion by the unit, there is sure to be great improvement. But (leaving aside occasional and probably inevitable episodes of epidemic spread) can surgical units reduce clinical infection to about 1–2% of clean surgical wounds, without distorting surgical and nursing practice in any way? If they could, this would be a great advance on the present state of affairs when sepsis-rates of around 10% are not at all unusual. Professor WILLIAMS and his colleagues estimate that, on the average, surgical wound sepsis keeps the patient in hospital about a week longer than is necessary, and they say that, if their conclusions are applicable to the $1^1/_2$ million operations performed in Britain each year, the annual cost is that of 1 million extra patient-days in hospital. Since this is the conclusion of an exceedingly cautious and conservative approach to the figures and possibilities, it must make us all profoundly hope and pray that the infection risks inherent in all hospitals are being fully taken into account in

1. Hospital Infection: Causes and Prevention. By R. E. O. WILLIAMS, R. BLOWERS, L. P. GARROD, and R. A. SHOOTER. London: Lloyd-Luke (Medical Books). 1960. Pp. 298. 35*s*.
2. Flemming, C. *Lancet*, 1959, i, 257.

planning new hospitals. Some plans that have been produced for " rationalising " the allocation of operating-theatres and reducing their size may well need re-examination in the light of what infection costs. Moreover, the enthusiast who crams all possible beds into his wards should take note of the simple affirmation that " the distance between bed centres should not be less than nine feet " (p. 191). Further thought, too, should be given to providing isolation for general surgical and medical patients who need it—a subject admirably set forth and judicially analysed here. This first challenge, therefore, is to the whole profession. It is in effect to each one of us to read the book and then consider his own role. Few will fail to discover ways in which they avoidably increase infection risks or neglect actions by which they could reduce dangers.

The second challenge concerns the space given to staphylococcal infection—three chapters being wholly devoted to staphylococci out of ten on the epidemiology of hospital infection. But, as the authors say, staphylococcal infection is the one which, in its many different forms, has caused most worry and perplexity in recent years; it is exceedingly common and sometimes fatal; the mode of transmission is still obscure; and the precautions which matter most in preventing it have yet to be certainly identified. Whether the epidemiological picture will be fundamentally altered by the penicillinase-resistant penicillin introduced since the book went to press we cannot yet be sure [3]: certainly the outlook for the individual infected patient is now much more favourable, but the general picture has not yet changed. Moreover, the authors deal faithfully with infections due to gram-negative bacilli, diseases of the urinary and intestinal tracts, tetanus, and gas-gangrene, and others of which some have doubtless been included mainly to keep the record straight. They have first-rate chapters on administrative control of hospital infection and on operating-theatre design and practice. Altogether, therefore, we may well decline this second challenge, fully acquitting the authors of having given too much time and thought to staphylococci.

When, however, they wonder whether they will be accused of " too agnostic an attitude ", their challenge must be taken up. They remark that in medicine it is easy to dogmatise and to dress up opinions in the guise of ascertained facts; and they are right to deplore such habits. But in some of their writing they can be held to express opinions which call for critical comment. For example, the use of water at 75°C or 100°C is more than once defended against critics who are supposed (one gathers) to advocate autoclaving because they fear that clostridial infection is often conveyed by boiled instruments, or even bedpans. But the case for the general use of the instrument autoclave or the ready sterilised and assembled syringe and needle does not in fact rest on such fears. The reason why boiling has been blamed is that it is often abused [4]: indeed in certain parts of their text the authors show themselves well aware of these abuses. When a sterile instrument or syringe is needed in a hurry—and that is not the exception—boiling is liable to be perfunctory; and what is found on culturing a poorly boiled rubber catheter is not merely sporing organisms but staphylococci and coliforms. (Hollow tubes of all kinds are more difficult to clean and to sterilise than most nurses and doctors seem to realise.) The authors show in chapter XVIII that they know how a hospital can benefit from central sterile supply and reliable autoclaving. Why then do they go so far out of their way to make points about the efficacy of adequate boiling which are well known to all but which still do not make the method advisable for hospital theatres and wards or inoculation clinics? However valuable boiling may be to the bacteriologist in his own laboratory, especially where he is his own technician, we cannot think it wise to appear to press for a method which, in the conditions actually prevailing in practice and in most hospitals, is wide open to abuse. Moreover, before the medical profession raises the bogy of costs of new procedures, it ought to ascertain the true price of all the wasted time, labour, destroyed decorations, and avoidable cross-infection that may be attributed to some of the mock-sterilisation rituals now being used. It should also discover whether an educated public opinion is in fact unwilling to pay the price for a real guarantee of sterility. Enough evidence of failure to sterilise is quoted by Professor WILLIAMS and his colleagues to trouble most doctors' consciences; and many of the residual problems of hospital infection may well be found to be psychological rather than technical. Surely we can agree on one simple rule: articles accepted as sterile must carry a valid guarantee of having been through an effective process of sterilisation.

Two other points for criticism—again probably the outcome of agnosticism—need to be mentioned:

Firstly, on p. 141 the spread of serum hepatitis (other than by transfusion) is said to be completely preventable by the simple rule that no needle that penetrates the skin of one patient is used for a second without being sterilised. This might fail to convey to some that any syringe attached to the needle will also have to be sterilised.

Secondly, on p. 168 the question whether refrigerated ventilation is necessary for operating-theatres in Britain is answered in the negative because in London the daytime maximum temperature exceeds 77°F on an average on only twelve days of each year and in Glasgow on only three days. Since the immediately preceding text correctly states that most British surgeons like an air temperature of 65–70°F, and since operating-theatres must contain a great many irremovable heat sources such as the patient, members of the staff, and lights, this dismissal of a difficult problem may well be found inadequate if the object is to provide tolerable conditions throughout an operating session lasting several hours.

The purpose of challenges is presumably to be accepted; but we take up this one only because we think that the agnosticism of which the authors speak in their preface may have created needless contradictions in their essential message, and that these contradictions could confuse readers who earnestly wish to do what is needed to make hospitals safer places.

3. *Brit. med. J.* Sept. 3, 1960; *Lancet*, Sept. 10, 1960.
4. Nuffield Provincial Hospitals Trust. Present Sterilising Practice in Six Hospitals. London, 1958.

Annotations

RETIREMENT OF SIR JOHN CHARLES

FROM this week we must cease to think of Sir John Charles as chief medical officer of the Ministry of Health.

Son of a general practitioner in a mining town of County Durham, he was medical officer of health for Newcastle when in 1944 he was invited to join the Ministry as one of Sir Wilson Jameson's deputies. In Newcastle—the city of his quietly brilliant university career—he had done much to raise standards of health, particularly in the slums, and with his friend James Spence had set on foot the now famous studies of the health and nutrition of children. At the Ministry his high intelligence and manifest sincerity again won the esteem of his colleagues. He showed himself a person of extraordinary patience, and to those trained in other disciplines he also conveyed something of the grandeur of medicine as a branch of learning—something of its particular tradition of intellectual integrity.

"He will be remembered," writes an associate, "not only as a learned man, with a distinction of mind which was a delight to all who had to do with him, but as a very wise one. Wisdom can be imparted in many ways. John Charles was at his best in unhurried discussion from behind his own desk with a perplexed colleague sunk in the depths of his official armchair. The solutions he then put forward had the simplicity and inspired common sense which mark wisdom in action."

In the World Health Organisation he found other and different scope, and he was recently president of the World Health Assembly. Alike in international and in national work, in public and in private affairs, his capacity for taking pains, and his constant wish to help, have been very valuable; and in earning respect he has gained also affection. With his special qualities still growing, retirement from one kind of service must mean only a change to another.

ON CLOSING A CRANIAL FISTULA

THE classical indications for closure of a craniopharyngeal fistula by a fascial graft were persistent cerebrospinal-fluid rhinorrhœa—an absolute indication—fissured fracture crossing the roof of a nasal sinus, anosmia, and meningitis following injury. With the advent of chemotherapy and antibiotics, meningitis became increasingly curable; and this complication became so lightly regarded that some patients were allowed to suffer repeated attacks before surgical closure of the fistula was attempted.[1]

Of late years reports have appeared of recurrent attacks after injury to the nasal sinuses [2 5] or the petrous bone [6 7] and operations on the nose or ear, or owing to congenital malformation. In traumatic cases the injury may have been sustained a long time before [3 8]—as long as thirty years [9]—while a history of rhinorrhœa and radiological evidence of fracture may be absent.[10 11] Both the delay in the onset of symptoms and the absence of rhinorrhœa are due to occlusion of the fracture line by a cuff of meninges with or without brain tissue.[12] Such a situation is dangerous in the event of upper-respiratory infection. Congenital malformations which lead to meningitis include nasal encephalocele, dermoid cyst or sinus, epidermoids, and persistent fœtal fistulæ—for example, through the petrosquamosal suture or foramen cæcum.

Bøe and Huseklepp [1] emphasise again that meningitis even long after a head injury should arouse suspicion of a fistula, and that recurrent attacks, in the absence of any other cause, warrant surgical exploration. They distinguish carefully between relapse and recurrence. Surgical treatment is by craniotomy with application of a fibrous sheet—usually autogenous fascia lata—intradurally over the breach in the dura and the bone. This treatment should be advocated clearly and firmly: despite their conviction of the need for surgical treatment, Bøe and Huseklepp persuaded only 2 out of 5 patients with recurrent meningitis to submit to operation. In these 2, injury to the roof of the nasal sinuses was found; this had not made its presence known in any way other than through the multiple attacks of meningits.

Of the surgical principles that have weathered the wind of antibiotic change, one is that a persistent cerebrospinal fistula should be closed.

HUMAN FLOTSAM

THE National Council of Social Service has published an interesting account [13] by Mr. Merfyn Turner of a common lodging-house in London. Most of the 300 men housed there were fairly long-stay residents: three-quarters of them stay for more than six weeks and half for more than six months, though a good number were continuously on the move. About 60% were in regular work (a high proportion for such places) and perhaps 25% had recent experience of prison—though the management liked to think the number much less. Some 20 men were of severely subnormal mind as a primary condition and about 12 were mentally ill—often quite grossly schizophrenic, so it seemed. Otherwise the community seemed to be made up of those shiftless, unreliable people often termed "inadequate psychopaths" with no stake in anything, no identifications, and no future, though a number of old-age pensioners were in slightly different circumstances. But lodging-houses tend to gather their own differing clientele.

Staff of lodging-houses with a religious (like this one) or philanthropic background usually had a clearer idea what they were trying to do, but the evangelistic rehabilitation ideals of the late 19th century could scarcely be achieved in this sordid environment. The superintendent and his 4 or 5 senior staff seemed to be quite able and concerned people, a group of lonely men united in their loneliness, living in very poor conditions on tiny salaries. The 20 porters-cum-cleaners were on a level with the lodgers. Rehabilitation, Mr. Turner says, is a matter of relationships, and the superficiality of these, staff with lodger, was the most consistently disappointing feature of the life. Reformative value seemed almost totally lacking, and even religious conversion—in this setting—was highly suspect. The policy of ignoring a man's past, while theologically sound perhaps, prevented the staff from coming to grips with the lodgers' basic problems. From lodging-house perspective, the National Assistance Board and charit-

1. Bøe, J., Huseklepp, H. *Amer. J. Med.* 1960, **29**, 465.
2. Traut, E. F. *J. Amer. med. Ass.* 1945, **129**, 273.
3. Hoyne, A. L., Schultz, A. *Amer. J. med. Sci.* 1947, **214**, 673.
4. Galloway, W. H., Chambers, W. *Lancet*, 1953, ii, 68.
5. Tribiano, C. W. *J. Pediat*, 1953, **42**, 609.
6. Maxwell, J. H. *Laryngoscope*, 1953, **63**, 355.
7. Prêcechtél, A. *Acta otolaryng. Stockh.* 1954, **44**, 427.
8. Winberg, J. *Nord. med.* 1955, **54**, 1288.
9. Stenger, H. H. *Z. Hals-, Nas.-u. Ohrenheilk.* 1958, **7**, 65.
10. Barsky, P. *Canad. med. Ass. J.* 1955, **72**, 210.
11. Ocklitz, H.-W. *Mschr.Kinderheilk.* 1955, **103**, 12.
12. Ectors, L. *Scalpel*, 1957, **110**, 809.
13. Forgotten Men. A Study of a Common Lodging House undertaken by the London Council of Social Service at the request of the Calouste Gulbenkian Foundation. National Council of Social Service, Inc. (ref. no. 587), 1960. Pp. 91. 5*s*.

able institutions seemed largely ineffective and their incentives (positive and negative) quite inadequate to make much impression on this type of man. A strong case could be made for firmer handling: corpus is often much too habeas, though today's prisons are not really the answer. Looking to the future, Mr. Turner has a few good (and, one fears, quite unattainable) ideas. Among other things, he would cut down the size of the houses to about 60, split up the vast dormitories to small units, employ casework and group techniques, train and upgrade the staff, and bring in women to help.

Forgotten Men gives the impression of a very valuable piece of research that has not quite come off. What could have been, as Mr. Turner intended, a valid factual study, with appendices, index, and a survey of the literature, has ended up a well-written journalistic fragment, decorated with a few case-histories and personal impressions. But the position of the researcher was evidently a difficult one, poised mid-way between staff and lodger, and it is easy to see that suspicion and prejudice made fact-gathering very hard indeed. The booklet is a work of social reform rather than of science, and it deserves to stir the public conscience.

METRONIDAZOLE IN THE TREATMENT OF TRICHOMONIASIS

METRONIDAZOLE ('Flagyl', 8823 R.P.) is a derivative of nitro-imidazole—namely, 1-β-hydroxyethyl-2-methyl-5-nitro-imidazole—which has been claimed to be an effective oral remedy for human genital trichomoniasis. Cosar and Julou [1] found that this drug was highly active against *Trichomonas vaginalis* in vitro, and in vivo in the mouse. There was little evidence of acute toxicity in mice, and no evidence of chronic toxicity when it was given by mouth to rats in amounts up to 50 mg. per kg. daily or to dogs in amounts up to 100 mg. per kg. daily for a month. Successful clinical trials in men and women were reported by Durel et al.[2 3] and by Sylvestre et al.[4] First reports from this country were presented to the Medical Society for the Study of Venereal Diseases last May.[5]

There is general agreement that in most cases of trichomonal vaginitis this drug, given by mouth, causes disappearance of the organism from the secretions within a few days and complete resolution of the vaginitis within one or two weeks. This satisfactory response occurred in 88–96% of cases.[6–9] In some cases the condition recurred during subsequent observation; but Rodin et al.,[6] who observed and tested 52 patients for three months after treatment, claimed ultimate success in 83%. Only 4 of their 82 cases failed to respond immediately, and in 2 of these there was evidence that the tablets were not taken regularly and that the treatment was not continued for the full period; in the other 2 cases serum levels of the drug, estimated by the polarographic method, were considerably lower than in cases successfully treated. Rodin et al. suggested that immediate failures of treatment might be related to low concentrations of the drug in the serum, owing to failure to take the tablets, or to some deficiency of absorption, or perhaps to abnormally rapid excretion in the urine. Of their 6 patients who later showed evidence of failure of treatment, in that the vaginitis returned and the organism reappeared, 5 admitted unprotected coitus and therefore the possibility of reinfection.

Recurrence of vaginitis after local remedies has been the rule rather than the exception, and has been attributed to reinfection from the urinary tract [10] or to reinfection from the male partner. Formerly *T. vaginalis* was seldom found in the urogenital tracts of men; but in the past few years investigations based on careful search and good cultural techniques have indicated that infection of males is commoner than had been supposed. Nevertheless the organism may still be hard to find in the infected male, and investigations as to incidence have yielded varied results. Catterall and Nicol [11] demonstrated *T. vaginalis* in all the female partners of 56 men with trichomonal urethritis, but Watt and Jennison [12] found the organism in the husbands of only 18 out of 30 women with trichomonal vaginitis. Treatment applied only to the female patients, even though successful, is likely to be followed by the appearance of relapse which is really reinfection. The results of treatment with metronidazole of men suffering from the disease have been reported in relatively few cases but seem remarkably good. There were no failures in 13 cases treated by Durel et al.,[3] in 15 treated by Sylvestre et al.,[4] in 20 treated by Rodin et al.,[6] and in 11 treated by Nicol et al.[13]

The dose of metronidazole commonly used is 200 mg. by mouth three times daily for seven days, although Nicol et al.,[13] in a preliminary report, described good results after only five days' treatment. No serious toxic effects have yet been described. Rodin et al.,[6] who observed their patients closely, noted mild gastrointestinal disturbances in 10 out of 82 women under treatment. Individual patients complained of dry mouth, of furred tongue, and of bad taste in the mouth. 1 patient had an irritating scarlatiniform rash on the arms on the day that treatment ended, and this spread to the chest and back. Of their 20 male patients, 1 complained of headache and depression but continued to take the tablets. In none of their cases was it necessary to discontinue treatment. Serial estimations of the total and differential white-blood-cell counts were done in 41 cases, mainly during the first two weeks of treatment. In 3 cases the total polymorph-count fell below 1500 per c.mm., which is usually accepted as the lower limit of normal, but in all 3 cases the levels had risen to well above the lower limit of normal at the next count. There were no associated symptoms. The drug appears to have had no ill effects on pregnant women.[6 8 9 14]

The use of metronidazole in the treatment of trichomoniasis is still in the experimental stage, and it would be unwise to draw final conclusions. There seems good evidence, however, that the drug is effective in the treatment of males and females, and up to the present toxic effects have been slight. There appears to be no indication for local treatment in the great majority of cases. There is overwhelming evidence that the disease is transmissible between the sexes, and it is essential that sexual partners should be examined and carefully tested for the presence of trichomonal and other infections. Diagnosis may present difficulties in the male; and, when a strong presumption of a shared infection exists but the organism

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cannot be traced in the male partner, there may be a case for treating him nevertheless.

Metronidazole promises to be a major advance in the treatment of a common and distressing condition which has hitherto resisted control. We hope that it will not be used indiscriminately and without proper investigation. Trichomoniasis is often associated with other genital infections, especially gonorrhœa and non-gonococcal urethritis and cervicitis. Associated conditions should be sought and treated and tests of cure applied, and sexual partners should be investigated and, if necessary, treated.

OXYGEN FOR CONVULSIONS

OUTSIDE hospital most convulsions take place in circumstances where there are no means of terminating the seizure, and treatment is usually limited to preventing the patient injuring himself. In the hospital ward, convulsions are often arrested by administration of potent depressant drugs. It is, however, in the operating-theatre that anticonvulsant therapy is most promptly applied. Most anæsthetists have seen either the so-called " late ether convulsions " or else convulsions as a toxic manifestation of local anæsthetic drugs. Termination of the convulsion by means of a small intravenous dose of a barbiturate has been an accepted form of treatment since 1936,[1] and thiopentone is nowadays the drug most often used for this purpose. It is at hand in the operating-theatre and can therefore be administered within a few seconds of the start of the seizure, which is usually arrested within little more time than the arm-to-brain circulation-time. Not uncommonly this treatment is followed by a period of apnœa requiring artificial ventilation.

Moore and Bridenbaugh [2] have reported 93 instances of convulsions in a series of 36,113 administrations of local and regional anæsthesia. They regard the convulsion as indicating a toxic reaction, the most important aspect of which is the subsequent depression of respiration and circulation; and this depression will be enhanced by administration of barbiturates. They recommend, therefore, that during a convulsion attention should be concentrated on the maintenance of oxygenation so that the subsequent stage of depression may be reached without hypoxia of the vital centres and without the added depressant effect of other drugs.

Attractive as may be the avoidance of drug therapy during the clonic stage, adequate oxygenation may become impossible despite administration of 100% oxygen by mask. Oxygen balance is doubly disturbed, with increased consumption due to muscular activity and uptake hampered by rigidity. Furthermore, previous underventilation may have already reduced the oxygen tension of the arterial blood to the point at which desaturation is evident. Under these circumstances ventilation is imperative, and Moore and Bridenbaugh recommend myoneural blockade with suxamethonium. The effects of this depolarising relaxant will normally pass off within a few minutes, leaving no residual impairment of respiratory or circulatory function. Curare was used in a similar manner as long ago as 1946 by Greenfield.[3]

It would probably be impossible to carry out in man a trial which would yield satisfactory evidence that one of these two forms of treatment is significantly better than the other. It is therefore largely a matter of personal preference whether to follow the established practice of arresting convulsions with a barbiturate, or to refrain from adding further chemicals to the bloodstream and to concentrate on maintaining oxygenation. Moore and Bridenbaugh claim that in their series of 93 convulsions there was no death which could be attributed to the toxic reaction to the local anæsthetic. It would be interesting to know whether their method of treatment is equally effective in the much more dangerous convulsions under general anæsthesia.

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SETTING A WHALE TO CATCH A SPRAT

THE risk of malignant changes supervening in certain proliferative epithelial lesions is clearly established. This risk can be averted by excising the whole of the proliferative area; and the problem for the pathologist who sees the precancerous changes in biopsy material (which usually represents only a part of the whole lesion) is to decide on the magnitude of the hazard.

Boddington et al.[1] have correlated and compared the clinical findings in 8522 gynæcological cases with the microscopical examination of 10,000 cervical smears and a lesser number of cervical biopsies (ring, multiple, or cone) or of the amputated cervix. A cytological classification for the smears had first to be devised. Seven grades were made: in the first, any suspicion of malignancy was ruled out; the next three covered the changes of early malignancy, and the last three those of advanced malignancy. Similarly eleven grades were devised for the histological examination of the biopsy specimens, the first seven indicating increasing grades of noninvasive " epithelial instability " and the last four grades of invasive carcinoma.

In the 129 cases where the cytological appearances of smears and the histological findings from biopsies could be compared, it was found that most histological grades had a corresponding cytological grade but that there was so much variation that the histological grade could not be reliably deduced from smears. Boddington et al. suggest that cytological changes in the smears reflect biologically important cellular changes, but that smears give no clue to the invasive properties of the deeper parts of the epithelium since they can represent only the superficial layer.

In the seven-year period of the investigation, 11 cases of clinically unsuspected invasive carcinoma were detected. In the same period 9 adequate smears were " false negative " for cervical carcinoma, and 14 were " false positive "—i.e., histological study revealed no cause for the abnormal cells. In addition, 67 cases of possible precancerous cervical abnormalities (grades 1–7) were detected; most had been clinically unsuspected. Invasive carcinoma was found in 3 of these cases at an interval of at least a year after the first smear, and in none did recurrence or death follow treatment. In 15 cases the abnormal cells disappeared and remained absent after biopsy, indicating either spontaneous regression or complete removal of the lesion, and in 3 others more than one biopsy was needed to eliminate the abnormal cells. In many more cases the course of the disease was interrupted by surgical treatment, and nothing more could be learnt from them. There remained, however, a group of 10 cases in whom, for various reasons, a persisting lesion was followed for periods of from two to five years. In 8

1. Boddington, M. M., Cowdell, R. H., Spriggs, A. I. *Brit. J. Cancer*, 1960, **14**, 151.

of these, abnormal cells were constantly present; but their character did not change, except in 1 case where there was a sudden change to a more anaplastic-looking type of cell; biopsy or hysterectomy revealed early carcinomas in 3. In 1 patient the cell type progressed from a lower to a higher grade, and on cervical amputation a lesion of advanced preinvasive histological grade was found. In the remaining case the abnormal cells persisted for a year and then disappeared.

Petersen [2] recognised lesions which carried a 30–40% risk of sooner or later becoming malignant; but Boddington et al. do not believe that it is possible to predict the course in any particular case. They insist that in all cases of cervical epithelial instability, however this is revealed, it is of the utmost importance to discover whether an early invasive carcinoma has been missed. They are convinced that cervical smears will not reveal such a condition, and recommend full histological study in every case. They regard it as unjustifiable to expect any cytological warning before invasion begins. They conclude that epithelial instability usually disappears without any treatment more extensive than biopsy, but that it sometimes becomes irreversible; and in this event invasive carcinoma sooner or later develops, without any cytological warning.

Thus about a third of lesions classed by biopsy as precancerous can be expected to become malignant within a year or two. Cervical smears may indicate that the lesion is persisting, but will not tell us when to wait or when to amputate the cervix uteri. Cervical smears may reveal a few cases of cervical carcinoma but will miss an equal number or suggest the presence of carcinoma when it is not there. As a research project the 10,000 smears have served their purpose. As a routine procedure, examination of cervical smears, perhaps undertaken with less care and skill than in this investigation, has yet to win an established place.

SMOKING AND RESPIRATORY DISEASE

THE extensive work carried out in the past decade on the association between smoking and respiratory disease has been reviewed by the Joint Tuberculosis Council of Great Britain.[3] As long ago as 1955, the majority of doctors had concluded that cigarette-smoking was responsible for a high proportion of lung-cancer deaths [4]; and the Council considers that the evidence is now conclusive. Cigarette-smoking has also been proved greatly to aggravate chronic bronchitis, and to impair respiratory efficiency in the healthy. Yet, even though for some years few intelligent laymen can have been ignorant of the sinister role of cigarette-smoking, the number of cigarettes sold continues to increase. Cartwright et al. found in an inquiry in Edinburgh that a large majority of both smokers and non-smokers expressed the view that smoking might affect the health of others; but only a minority of smokers considered that the habit had harmed them personally.[5] The Council believes that doctors have a moral obligation to put the facts before the public; and most doctors do seem fully conscious of this responsibility. Data from 85 chest hospitals and clinics indicate that in 60 of them physicians still addicted to tobacco now refrain from smoking in front of patients; and it is likely that other sections of the profession also appreciate the value of example.

But, while the profession should take every opportunity of declaring that smoking menaces health, only effective Government action can decisively influence the general public's attitude. In the light of present knowledge, as Fisher [6] has emphasised, it would be hard to justify the Government's continuing laissez-faire policy towards the skilful and sustained propaganda campaign for smoking conducted by the tobacco industry. Something must be very wrong when, against the background of a rising death-rate from smoker's cancer, a company can proudly proclaim on television spectacular increases in its cigarette sales.

Clearly, anti-smoking campaigns [7] will not induce established smokers to give up the habit; and that is why it is so important to prevent young people from developing this habit. The health education officer of Middlesex, Mr. W. G. Penn, recently interviewed 2500 schoolchildren in the county to find out their attitude to smoking.[8]

Boys who smoked started on average at the age of 9 years and girls at 13. Most of the heavy smokers were pupils of lesser ability in secondary modern schools. They had no difficulty in obtaining cigarettes; some retailers stock packets of 4 for 6*d*., and others sell single cigarettes or even halves. They began to smoke usually with others in their home district, rather than with their school companions.

In prevention, example was rated highly by the children. But three-quarters of them stated that they would accept factual information combined with intelligent persuasion from those they trusted, even if these adults were smokers themselves, provided the adults made it clear that data on the disadvantages were not available when they themselves started smoking. Talks on the subject at school were not popular; but science periods, possibly with practical work, or discussion groups, would be acceptable. Leaflets were ineffective: children did not read them. Posters, with one exception—showing a single cigarette with "cancer" spelt out by its smoke—made little appeal.

On the negative side, cigarette advertisements on television exerted an influence, but this could be readily dispelled by ironic ridicule.

Children appreciate the approach designed to shock them into taking notice—"I don't care if you smoke yourself to death, but if you do smoke you should know the facts". They declared they would gladly watch a film, and, when asked to select a possible plot, chose the one with this approach.

Mr. Penn recommends that the law prohibiting under-16s from buying cigarettes should be more widely publicised and enforced; and he points to a loophole in legislation: this age-group is not prohibited from smoking, but only from obtaining, cigarettes. Mathematics teachers, says Mr. Penn, should be encouraged to use the figures on smoking and lung cancer when setting problems. Posters prepared by the children themselves in art classes could be used for a permanent but changing display. Schools' broadcasting and television, he concludes, should at least once a year include programmes on smoking.

We agree with the Joint Tuberculosis Council that a policy designed both to reduce cigarette-smoking and, above all, to discourage young people from starting to smoke should be agreed and implemented without delay.

Viscount AMORY, formerly Chancellor of the Exchequer, has been appointed a member of the Medical Research Council, and will succeed the Earl of Limerick as chairman.

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Special Articles

TREATMENT OF RESPIRATORY PARALYSIS IN SMALL CHILDREN

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DURING the summers of 1957 and 1958, 11 children, aged from six months to four years, with respiratory paralysis caused by acute poliomyelitis were admitted to the Peterborough Isolation Hospital. This is an uncommon condition in the very young, and it is hoped that an account of our experience may help others faced with the same problems.

In 1957, 32 patients with poliomyelitis were admitted to the hospital. 16 of them were children under fourteen. 4 children, all under four, had respiratory paralysis.

In 1958, 10 patients with poliomyelitis were admitted. There were 2 adults and 8 children. 7 of the children, all under three, had respiratory paralysis.

Thus, out of a total of 42 patients, 11 (26%) were children with respiratory paralysis. There were also 2 adults with respiratory paralysis, making a total of 13 (31%) respiratory cases. Of all these, in both years, only 1 child had been immunised against poliomyelitis, having received his second injection three weeks before the onset of the illness.

As all cases of poliomyelitis in the area are admitted to this hospital it can be seen that, especially in 1958, there was a high incidence of respiratory paralysis among the younger children. This contrasts with the finding of Kelleher et al. (1956) who, in a series of 70 cases of acute respiratory poliomyelitis, had no case under one year, 1 under two years, and 7 under five years. Neonatal cases have rarely been reported, but McMath (1959) describes a successfully treated case and reviews the literature.

SUMMARY OF CASES

—	Case	Age (years months)	Paralysis: Intercostal	Paralysis: Diaphragm	Paralysis: Other	Time in respirator (weeks)
1957	A	2 11	+		legs	15
	B	2 11	+		arm	12
	C	4 0	−	+	..	9
	D	1 0	+		legs	10
1958	E	1 1	+		arms and legs	19
	F	0 6	+		back	39
	G	1 6	+		..	21
	H	1 11	+		legs	18
	J	1 6	+		..	10
	K	1 5	+		legs	39
	L	1 1	+		legs	21

The accompanying table summarises our cases.

There were also 2 cases of " bulbar " poliomyelitis, but these are not included among the respiratory cases, and none of our respiratory cases had bulbar involvement.

Diagnosis

Respiratory weakness may come on slowly or quickly and at a variable time in the course of the illness. The signs, symptoms, and diagnostic tests have been well described by others (Trueta et al. 1956, Kelleher et al. 1956); but with small children the cooperation of the patient cannot be relied upon, and special tests such as counting and spirometry cannot be used. It may, therefore, be difficult in the early stages to decide whether a child is developing respiratory weakness. These points have seemed to us the most helpful:

(1) *The appearance and behaviour of the child.*—At first the child is restless and fretful. As the condition progresses, he becomes quieter and weaker but remains wakeful and worried—the " unsleeping apprehension " which Trueta describes. The skin may be clammy and pale, and slight cyanosis, difficult to detect by artificial light, sometimes occurs. Marked cyanosis is a late sign which occurs only when anoxia is severe. The pupils may be dilated, and the pulse-rate and respiration-rate raised.

(2) *Respiratory movements.*—The respirations become rapid and shallow and, unless the diaphragm is weak as well, there is more abdominal than thoracic movement. The upper end of the sternum is drawn inwards with each inspiration, causing a sort of seesaw movement of the sternum. In more severe paralysis the accessory muscles of respiration come into use. When intercostal paralysis is unilateral or asymmetrical, the difference in movement between the two sides can often be seen. Sometimes it is best appreciated by placing both hands round the chest and by feeling the difference rather than by seeing it.

(3) *Pulse- and respiration-rates.*—Hourly charts, which were of great value, were kept for the first few days in all suspected and established cases of poliomyelitis. A rising pulse- or respiration-rate was often an early sign and, in a few cases, it gave us the first indication of respiratory weakness. An increasing respiratory-rate is more significant than a rising pulse-rate.

(4) *Biochemical investigations.*—Capillary blood-pH determinations and oxymetry were both used, but were not much help in diagnosis. They were more useful in the assessment of proper ventilation while in the respirator, and will be discussed later. In those cases in which the blood-pH was estimated before putting the child in a respirator, it was never more than 7·2 and it always rose quickly once respiration was assisted. Thus it gave some confirmation of the need for going into a respirator.

Treatment

Going into a Respirator

One may feel reluctant to put a child in a respirator when the signs are slight and the diagnosis uncertain. The following considerations may help:

(*a*) Every case of ours developing respiratory weakness eventually needed treatment in a respirator.

(*b*) Of the signs and symptoms already discussed, changes in the chest movements are probably the most important, and careful and repeated observation is needed to detect them.

(*c*) The respirator may act as a splint for the respiratory muscles. Active use of any muscles during the early stages of the disease increases the risk of paralysis in those muscles, and it seems likely that when there is even slight weakness in some of the respiratory muscles the extra strain on those still working normally may dispose to a more severe paralysis.

We have concluded, therefore, that once respiratory weakness has been diagnosed, the child should be put into a respirator without delay. If there is any doubt, the child should be kept under constant observation by a nurse and frequently examined by a doctor with experience of poliomyelitis cases. It is better to err on the side of safety by putting the patient in early than to risk leaving it too late. Unpredicted rapid deterioration and collapse can occur, and we had an alarming instance of this. Often all doubt was dispelled by seeing the obvious improvement in the child, who after a brief period of anxiety and resistance, settled down gratefully and peacefully to sleep.

Management in the Respirator

All our children could be taken out for short periods. This simplified nursing problems considerably. A watch was kept for retention of urine in the early stages but none of our patients was troubled by this. Constipation was often a minor problem, particularly early in the illness when we were trying to get fæcal samples for virus investigation. The condition was best treated with glycerin suppositories.

A good friction-free seal at the neck is important and the most effective was a dry pad tied round the neck before applying the standard overlapping sponge-rubber collar. An ordinary sanitary pad, with, if necessary, a little of the wool-filling removed, was found satisfactory. In the earlier cases, ' Vaseline ' gauze was tried but the children's necks became sore. Necks were never sore when dry pads were used. At first, we found that there were no rubber collars available small enough for a baby's neck; but, once the need was known, these were readily obtained.

Apart from coping with the physical problems of nursing a small child in a respirator, there are more subtle but equally important aspects of nursing which cannot be ignored. Overcoming the initial fears of children and parents, keeping up morale, and maintaining the happiness of the patients during an illness of this sort is no easy task. We had a few psychological problems but none was serious. For this relative freedom from trouble, we are much indebted to the nursing staff, none of whom had special experience of this type of nursing, and few of whom were " children-trained ".

Records

Detailed record-keeping by the nurses was found to be of the greatest help. Each patient had a book of his own in which hourly records of the pulse and respiration were kept; the pressure changes in the respirator were noted and a detailed report made. This was not only of value in assessing progress but ensured constant and detailed observation of the child. It was also one way of helping to train a team of nurses in the management of respiratory paralysis.

Types of Respirator

All the children have been nursed in the standard, modified Both respirator, and this has proved satisfactory on the whole.

The youngest child was transferred after a few weeks to a Smith-Clark junior respirator, as he seemed unable to breathe well in time with the bigger one. The junior respirator, with its higher rate, may be the apparatus of choice in children under three.

One alteration suggested is that the front wall of both types of respirator, through which the neck passes, should be made of transparent material. It must be frustrating for a child to handle his toys without seeing them, or to see them without being able to handle them—perhaps for months on end.

Respirator Rates

It is best with small children to start with the quickest rate attainable and to slow down if necessary. This was 28 per minute on the Both respirator and 32 on the Smith-Clark. In fact, our patients all settled happily at these maximum rates.

Respirator Pressures

On first going in, relatively high pressures were needed, especially when the child was awake. Occasionally, it was impossible to get a crying child to breathe with the machine at all; while he was crying the accessory muscles were being used and breathing was quite independent of the respirator and in opposition to it. Soon he would become exhausted and would need, and respond to, help from the respirator. A sedative, such as chloral, was often helpful.

Typical pressures used were −15·0 mm. Hg while awake and −10·0 mm. Hg during sleep. Positive pressures were not used, although the gauge on the apparatus usually swung over to +2 mm. Hg.

Coming out of the Respirator

All the children we have treated have been able to tolerate short periods out of the respirator, but it was not easy to decide when the length of time out could be increased. We thought it unwise to try any increase during the first three weeks. After this, the time out was gradually increased, the child himself being the best guide to progress. In some children it was immediately obvious if they were out for too long: they quickly became pale and tired, and, as soon as they were put back again, lapsed into sleep. Others were less easy to assess and we soon learnt to rely largely on the opinion of the sister-in-charge as to whether they had been out too long. Looking tired was the commonest sign, and we tried to adjust the time out so that the child was put back before any signs of strain occurred.

Later, when we had a better idea of an individual child's behaviour, he was deliberately left out for as long as it was judged that he could tolerate. This test period was tried about once a week and, if used with care, was a useful guide to how quickly we could increase the time out, the object being to find the maximum period, short of intolerance. Once a child had been out for several hours at a time, he could soon be left out for the whole day.

The increase in time was, therefore, done cautiously and slowly at first and more quickly later. One particular child showed delayed effects of being out of the respirator for too long. He seemed well immediately after a test period of several hours, but looked tired, pale, and unwell for the next two days. In this case, oxymetry showed clearly that he had been underbreathing, although there were no immediate clinical signs. This delayed reaction was exceptional and on the whole there was a good correlation between clinical findings and oxymetry results.

Biochemical Control

In adults the estimation of vital capacity by spirometry may be used for initial diagnosis or for assessment of ventilation while in a respirator. This was considered impracticable with very young children and we did not try it, although Walley (1959) described it as a helpful procedure in an eighteen-month-old child. The rebreathing method of estimating alveolar pCO_2 (Campbell 1960) may prove to be valuable.

After consideration of the investigations available to us at the time, we decided that oxygen saturation and blood-pH were the most useful and caused least distress to the child; these were carried out on all our patients.

Oxygen Saturation

Oxygen saturation was estimated by means of a ' Stanco ' oxymeter mark 2, using the lobe of the ear treated with a rubifacient. The results obtained in this way were not necessarily accurate, but any change which occurred before and after a child was placed in, or taken

out of, a respirator gave a good indication of whether ventilation was adequate.

The oxygen saturation of the blood does not fall much until a considerable degree of respiratory failure has occurred and its greatest use was in assessing how much time could be allowed out during the "weaning" period.

A falling oxygen-saturation during a given period indicated that the child had been out of the respirator long enough, the fall occurring before the clinical signs of fatigue set in. It was also used as a check on under-ventilation while in a respirator.

Blood-pH

This was measured on a heparinised capillary sample taken under paraffin. 0·5 ml. or more was taken from an ear lobe and made up to 5 ml. with distilled water. The estimation was made on a Pye pH-meter. The sample was particularly easy to obtain if it was taken soon after the rubefacient mentioned above had been applied.

The results obtained confirmed the diagnosis and helped us in the early stages of treatment to find the optimum respirator-pressure and to avoid hyperventilation. Later frequent estimations were unnecessary.

Physiotherapy

Physiotherapy was started for the affected muscles, other than respiratory, as soon as the acute phase of the illness was over. The age of our patients made active physiotherapy for their chests difficult, and one of our greatest assets was a skilled pædiatric chest physiotherapist. Very young children soon acquired a habit of abdominal breathing which persisted after recovery of the chest muscles, and recovery of chest movements was delayed long after it seemed that there was a reasonable return of power to the intercostals. Once the child could be re-educated in correct breathing there was often a rapid improvement.

We have had much discussion with our colleagues about the use of abdominal binders. We think now that one function of the respirator is to protect the intercostal muscles from movement by acting as a splint. We have been content to allow free abdominal movement and have observed that in a respirator the movement is almost entirely abdominal. Later, when we have wished to encourage active chest movements, a binder was applied in some cases but it is doubtful if this can be made to reduce the diaphragmatic excursion without also restricting movement of the lower ribs. Some sort of corset is needed which will fit over the anterior abdominal wall and up into the epigastrium without constricting the lower part of the chest. An attempt was made to construct a suitable corset but it seemed of little use.

The opposing view is that thoracic movement should be encouraged, and abdominal distension avoided, by early application of a binder. Abdominal distension does occur, but in our children it was not troublesome and follow-up has shown that it never persisted.

Follow-up

All the children have been followed up and are doing well. They are all out of respirators and living a normal life at home, apart from the unfortunate few with other paralyses. Prophylactic penicillin or sulphonamides have been given to protect against respiratory infections. It is difficult to say how much good this has done, but none of them has had a severe infection since returning home, and more than one parent has remarked on the relative freedom from colds.

Teamwork

Finally, we would like to stress the importance of a combined team in caring for these difficult cases. Anæsthetists, orthopædic surgeons, pathologists, physiotherapists, nursing staff, engineers, and electricians all have much to contribute, and we have been especially fortunate in being able to call freely on our colleagues for help and advice. Much of what we have learnt, and reported here, is the result of our combined experience, and of discussion with others of individual problems as they arose.

Summary

The diagnosis of respiratory paralysis in young children and its treatment are discussed. The main points which arise out of our experience with these children are:

(1) The importance of early diagnosis of respiratory paralysis and the early use of a respirator.

(2) The value of clinical observation and the limited use of biochemical investigations in diagnosis.

(3) The function of the respirator as a splint as well as an aid to respiration.

(4) The importance of teamwork, and of skilled nursing and physiotherapy.

We have had help from many quarters, but we are especially grateful to Dr. R. E. Loder, consultant anæsthetist; Mr. Noel Smith, consultant orthopædic surgeon; Sister Course and the many nurses who have worked under her; and Miss Hardy and her fellow physiotherapists.

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STERILISATION BY STEAM UNDER INCREASED PRESSURE

A SECOND COMMUNICATION TO THE MEDICAL RESEARCH COUNCIL BY THE WORKING PARTY ON PRESSURE-STEAM STERILISERS *

THE working party began its investigations in 1957 and early last year published a report [1] which re-examined the requirements for efficient sterilisation by steam under pressure, described the principles and technical procedures of sterilisation by this method, and discussed their practical application. Since that time more information, some of it yet to be published, has become available, and further comment on four matters of immediate importance may be helpful.

(1) *High-vacuum Dressing Sterilisers*

The need for an initial vacuum down to an absolute pressure of 20 mm. Hg or less has been confirmed by several workers and this recommendation is now incorporated in two recent specifications by the British Standards Institution.[2] Well over 100 such sterilisers have been installed in the United Kingdom

*The members of the working party are: Prof. J. W. HOWIE, M.D., chairman, Dr. V. D. ALLISON, Dr. J. H. BOWIE, Mr. E. A. BRUGES, PH.D., Dr. E. M. DARMADY, Dr. R. J. FALLON, Prof. ROBERT KNOX, M.D., Dr. J. A. V. SHONE, Mr. G. SYKES, M.SC., Prof. C. A. WELLS, F.R.C.S., Mr. G. A. P. WYLLIE, PH.D., Dr. J. C. KELSEY, secretary. Address: Disinfection Reference Laboratory, Central Public Health Laboratory, Colindale Avenue, London, N.W.9.

1. *Lancet*, 1959, i, 425.
2. B.S. 3219:1960 Horizontal Cylindrical Hospital Sterilisers; B.S. 3220:1960 Horizontal Rectangular Hospital Sterilisers.

and experience indicates that, in general, they are proving bacteriologically efficient and mechanically reliable, though with increasing experience minor modifications in constructional detail are being made. The working party wishes to emphasise the potentially greater output, of a high-vacuum steriliser, as compared with other apparatus of the same cubic capacity. Accordingly, when planning for new equipment, the new machine may be of much smaller cubic capacity than the old.[3] Planners should take into account the present trend towards the centralisation of sterilising capacity within a central sterile supply service. In this way space can be saved and expensive equipment utilised fully.[4]

(2) *High-speed Instrument Sterilisers*

Several of these sterilisers have been installed and we understand they are proving satisfactory in practice. A British Standard[5] has now been published concerning this equipment.

(3) *Air Filters*

In the earlier report attention was drawn to the need to filter the air used to break the vacuum at the end of the sterilising cycle. After examining as yet unpublished work, the working party offer the following suggestions:

(i) *Filter material.*—Filters made of spun glass withstand the wear and tear involved and, if the right grade is chosen, are very efficient. At present glass fibre felted into sheet form of paper thickness offers the best prospects.

(ii) *Penetration.*—The methylene-blue penetration should be not more than 0·003% and could easily be as low as 0·001% without undue increase in resistance.

(iii) *Support.*—The filter material must be held firmly between metal grills for support, to prevent distortion, and to ensure uniformity of efficiency at all air flows. The space requirement for a filter built on these lines is negligible.

(iv) *Filter canister.*—This must be of stout construction in a metal which does not readily corrode (e.g., stainless steel or tin-plated brass).

(v) *Flow control.*—The incorporation of a critical orifice to ensure uniformity of flow and prevent excessive strain on the filter would be advantageous and very easily applied.

A filter built on these lines might be expected to have a working life of at least 12 months before requiring to be re-packed and need cost little, if anything, more than many filters now in use which are of much lower efficiency. At least two filters which approximate to this specification are already available commercially.[6]

The use of cotton-wool in cups or tubes cannot now be considered as more than an interim measure. The wool, which must be sterile and dry, needs to be changed frequently and unless it is firmly compressed channels form in it with loss of filtration efficiency.

(4) *Sterilisation of Rubber Gloves*

Work on this subject is in progress in several centres. The information available to the working party to date indicates that gloves may be sterilised in a high-vacuum steriliser at 130–134°C along with dressings, without suffering undue damage.

Great interest in hospital sterilising arrangements has been stimulated by recent publications, including the first report of the working party. It is now clear that the technical requirements for safe and efficient sterilisation by steam under pressure have been well defined, and the four matters of current interest discussed above confirm the views previously expressed by the working party, in particular the requirement for a high pre-vacuum for the sterilisation of dressings.

3. *Lancet*, Sept. 17, 1960, p. 643.
4. *ibid.* p. 353.
5. B.S. 3233:1960 Pressure Steam Sterilisers of Small Size (with Independent Steam Supply).
6. E. N. Mackley & Co., Hawks Road, Gateshead 8, Co. Durham; Vokes Ltd., Henley Park, Guildford, Surrey.

GENERAL MEDICAL COUNCIL

SESSION NOV. 22–26

IN a presidential address at the opening of the Council's 201st session, Sir DAVID CAMPBELL recalled that both the Council and the Pharmacopœia Commission had been invited to submit evidence to a working party established by the Minister of Health, in consultation with the Home Secretary and the Secretary of State for Scotland, "to review the legislative provisions which relate to the control of medicinal substances, and to recommend what changes should be made to rationalise and simplify the law with a view to ultimate amendment and consolidation".

At present there was no comprehensive and unified system of statutory control of medicinal substances. Many separate controls had been established piecemeal over the years, and were administered by a number of bodies, including the Dangerous Drugs Branch of the Home Office, the Poisons Board, the Ministry of Health, the General Medical Council, and the Pharmaceutical Society. In addition to such statutory controls, certain books of standards prepared on a voluntary basis by the Pharmaceutical Society and the British Medical Association jointly had received official recognition, while other official bodies, such as the Standing Joint Committee on the Classification of Proprietary Preparations and the Joint Committee on Prescribing, had been established for special purposes in the National Health Service.

Under Section 47 of the Medical Act, 1956, which re-enacted provisions going back to the original Act of 1858, the Council was responsible for the publication of the *British Pharmacopœia* which must contain "descriptions of and standards for . . . medicines, preparations, materials and articles used in the practice of medicine, surgery, and midwifery".

After full consideration and mutual consultation, the Council and the Commission had reached the conclusion that, as a consequence of recent developments in pharmaceutical practice, it had become desirable to change some of the procedures followed in regard to the *British Pharmacopœia*. Memoranda conveying the views of the Council and the Commission had been conveyed to the working party, which were in substantial agreement.

One of the recommendations related to the status of Approved Names. Since 1940 it had been the practice of the Council, acting on the recommendations of the Commission, to announce from time to time the names by which certain drugs would be described if they were subsequently included in the *Pharmacopœia*. Experience had shown, and the interim report of the Hinchliffe Committee on the Cost of Prescribing had recently attested, that the regular and prompt publication of Approved Names served more than one useful purpose. It helped to avert the use of a number of different names for the same active substance; and it served to protect as far as possible a suitable name from proprietary adoption as a trade mark.

This practice, however, was unofficial. The Commission and the Council thought that, if changes in the law were contemplated, it would be appropriate to accord them statutory recognition. They had accordingly recommended that the Council should receive statutory authority for the issue of Approved Names; and that,

while manufacturers should of course be left free to use their own proprietary names, it should not be legal for them to use any unofficial non-proprietary name for a drug other than the Approved Name. They had also recommended that manufacturers should be required to indicate the Approved Name of any drug on the labels of the medicine or preparation, and in all advertising matter. Such a provision would guard against confusion without seriously inconveniencing the manufacturer.

The inclusion of a drug in the *Pharmacopœia* had come to be widely accepted as an indication that it was therapeutically reliable; and a number of regulations and provisions, both in this country and overseas, had been framed on this assumption. The Council did not wish to disturb this situation. At the same time it was conscious that the necessary intervals between the publication of new editions and addenda sometimes caused considerable delay before a pharmacopœial standard was provided for a drug newly introduced into medical practice. As a result, some drugs and preparations were widely sold before independent standards had been provided.

In these circumstances the Council had been impressed by the view, which was strongly held by the Commission, that in the public interest standards should be made available for all drugs at (or very soon after) the time when the drugs began to be used in medical practice. It was true that under the provisions of section 47 of the Medical Act the Council was at present empowered to publish amendments of, and additions to, the *British Pharmacopœia* at any time; and it would be legally in order for it to publish, in the form of addenda to the *Pharmacopœia*, monographs for drugs as soon as they were placed on sale. It was advised, however, that such a course would not be equitable, or indeed practicable, in present circumstances. The Council and Commission accordingly had made a number of suggestions designed to enable the Council to publish, as Approved Specifications, standards for all newly introduced drugs as soon as, or within a short period after, the drug was placed on sale in the United Kingdom. These Approved Specifications would have a definite legal status of their own similar to, but distinct from, the standards given for drugs included in the *British Pharmacopœia*. The *British Pharmacopœia* would also continue to be published as at present; and some, but not all, of the drugs for which Approved Specifications had been issued would eventually be absorbed into it.

The evidence submitted also touched on two other important topics. The first of these related to the statutory authority of the standards contained in the *Pharmacopœia*. This was mainly a legal question. After comparing the law in this country with that in certain other countries the Council had recommended that the law should be amended to provide that in the United Kingdom any drug which was prescribed or demanded under a title or subsidiary title used in the *Pharmacopœia* should comply with the relevant requirements stated therein.

The evidence also dealt with the question of ensuring identity of the standards prescribed in the *British Pharmacopœia* and the regulations of the Therapeutic Substances Act. Under existing arrangements it had been possible for divergencies to occur in the standards prescribed for the same substances in the *British Pharmacopœia* on the one hand and the regulations made under the Therapeutic Substances Act on the other. In order to avoid such an undesirable duplication of standards, the Council and the Commission had recommended that the Therapeutic Substances Act, or the regulations made thereunder, be amended at the earliest opportunity so as to provide that, where any substance covered by part I of the Act was included in the *Pharmacopœia*, the standards to be observed in respect of that substance, and the tests to be used in determining whether those standards had been attained, should be contained in the *Pharmacopœia*.

Presenting the report of the Pharmacopœia Committee, Dr. H. GUY DAIN, its chairman, said that sales of the last *British Pharmacopœia* and the last *Addendum* (32,024 and 4970), compared with those of the previous *Pharmacopœia* and *Addendum*, showed a considerable falling off in accordance with the alteration in retail pharmacy, which would continue. There was not the same need for the retail pharmacist to be in possession of the *Pharmacopœia*, which set out the standards for making up prescriptions, because he was supplied by the manufacturer with drugs to the laid-down standard.

Turning to the section of the Pharmacopœia Commission's report which stated that the Commission continued its efforts to make possible the abandonment of the apothecaries system of weights and measures in the next edition, Dr. Dain explained that the change could not be made without an Act of Parliament because under the present law the pharmacist must do exactly what the prescription stated and it would be impossible for him to dispense in the metric system a prescription made out in the apothecaries system. The Government's new weights and measures Bill introduced the metric system not only for medicine but for everything else, but this would not be put into effect before 1967. " We are anxious to make the progress we want to make in 1963", continued Dr. Dain, and he announced that Lord Cohen of Birkenhead had undertaken to move an amendment in the House of Lords.

The revision of legislation concerning medicines was, said Dr. Dain, " a matter on which we are not too happy ". The control of medicines was governed by a number of Acts, and the Government had set up an interdepartmental committee to look at the matter, but the terms of reference were so wide that some anxiety was felt as to what might emerge. The Council itself and the Pharmacopœia Commission had issued their views to the committee, but they were very anxious that everything should be done to consolidate the Acts and make sure that the position of the *Pharmacopœia* and the Commission in the matter was properly assured.

At its May meeting in 1959 the Council asked each licensing body and medical school to submit not later than March 31, 1960, a statement with regard to its courses of study and examinations, together with an indication of any changes which had been made or were under consideration for the purpose of giving effect to the revised recommendations. Last May the Council gave preliminary consideration to the statements so far received and decided to adjourn further consideration until the present meeting. But the PRESIDENT announced that not all the licensing bodies and medical schools had yet submitted statements. At his suggestion a committee of deans and former deans was set up to analyse the statements and extract from them anything in the nature of a new approach and to report to the May, 1961, meeting.

Medical Disciplinary Committee

The committee met on Nov. 23–26, under the chairmanship of the President.

APPLICATIONS FOR RESTORATION

The Registrar was directed to restore to the Register the name of ALEXANDER GORDON BONNYMAN. The committee refused the applications of JOHN BODKIN ADAMS and PETER WILLIAM SPENCER GRAY.

REMOVAL FROM REGISTER

HAROLD JOHN SALTER, registered as of Oakwood Hospital, Maidstone, Kent, M.B. Lond. (1954), was charged with behaving improperly to and committing adultery with a woman patient. The committee determined the facts alleged proved to their satisfaction that the doctor was guilty of infamous conduct in a professional respect, and directed the Registrar to erase from the Register the name of Harold John Salter. He has 28 days in which to appeal to the Privy Council.

JAMES ALBERT DE GREGORY, registered as of Tudor Villa, Vaughan Street, Rhyl, Flintshire, M.B. Edin. (1931), was alleged to have been the family doctor of a man and his wife and subsequently of their three children and continuing to stand in professional relationship with the woman until Dec. 9, 1958, when her name was transferred, and with the remaining members of the family. It was further alleged that after he had entered into professional relationship with the man and wife and their family he improperly associated with the wife and from a date in or about December, 1958 (subsequently amended to July, 1959) he frequently committed adultery with her, and that he was found guilty of adultery with the woman by decree of the divorce court made absolute on May 25, 1960. The committee found Dr. De Gregory guilty of infamous conduct in a professional respect in regard to the facts found proved against him and directed the Registrar to erase from the Register the name of James Albert De Gregory. He has 28 days in which to appeal.

WILLIAM DAVID SMITH, registered as of 118, Marlborough Park Central, Belfast, M.B. Belf. (1940), originally had judgment postponed for a year in November, 1957, following convictions in 1956 and 1957 for being in charge of a motorcar while under the influence of drink or drugs. In November, 1958, the committee were not satisfied that the evidence so far received would warrant their discharging the case and postponed judgment for a further six months. At the meeting in May, 1959, a further charge of driving while under the influence of drink was proved. In order, however, to give him one further opportunity of overcoming his tendency to indulgence in drink, judgment was postponed for a year. Last May the committee were informed of a further charge of being drunk in charge and postponed judgment to the present session so that they might be aware of the result of these proceedings. He had been convicted of this offence at Oxford Quarter Sessions and sentenced to three months' imprisonment, ordered to pay £50 costs, and disqualified for 10 years. Announcing that the Registrar had been directed to erase from the Register the name of William David Smith, the chairman said: "The committee think on the whole that it is a kindness that they should remove your name from the Register for the time being, but if you come before them again cured of your addiction to drink, application for the restoration of your name to the Register will be sympathetically considered." Dr. Smith has 28 days in which to appeal.

ARCHIBALD THOMAS MACMASTER GLEN, registered as of 25, Santos Road, London, S.W.18, L.R.C.P.E. (1935), had judgment postponed for a year in May, 1959, following convictions in that year for driving a car under the influence of drink and being drunk and disorderly, the chairman saying that in the light of his previous record the committee regarded with grave concern the further offences of which he had been convicted. When he came for postponed judgment he had been convicted again of being drunk and disorderly. The case was adjourned for a further six months. A further charge was now found proved, of being drunk in a public place, for which he had been fined 20*s*. at the South-Western Magistrates' Court last July. The Registrar was directed to erase from the Register the name of Archibald Thomas Macmaster Glen, the chairman telling him, in similar terms to those used in Dr. Smith's case, that they thought on the whole this was a kindness. He has 28 days in which to appeal.

MRS. GRACE ALISON MCCORMACK, registered as of 70, Cheriton Square, Balham, London, S.W.17, M.R.C.S. (1940), was charged with having been convicted at Coalville Magistrates' Court in 1955 on four charges of unlawfully procuring dangerous drugs and one of failing to keep a Dangerous Drugs Register, for which she was fined £125 and ordered to pay £6 15*s*. costs, and infamous conduct in a professional respect in that she had between various dates in December, 1958, and January, 1959, obtained morphine at Bundarra, New South Wales, for the purpose of gratifying her own addiction, by fraudulently representing that she had prescribed them for various patients, and at Bundarra administering morphine to herself, to which offence against the Police Offences (Amendment) Act, 1908, of New South Wales she had pleaded guilty. Ordering the erasure of the name of Grace Alison McCormack from the Register, the chairman observed that this did not prevent her from applying for restoration if she was cured. She has 28 days in which to appeal.

JAMES ALBERT SEAVERS, registered as of 45, Clerkenwell Close, Finsbury, London, E.C.1, M.B. N.U.I. (1939), was charged with having been convicted of indecent assault for which on Aug. 22, at Lambeth Magistrate's Court, he was sentenced to three months' imprisonment. By reason of the conviction the Registrar was directed to remove from the Register the name of James Albert Seavers. He has 28 days in which to appeal.

CASE DISMISSED

ANDREW EDWIN BEITH, registered as of 17, Lincoln Street, Leicester, M.R.C.S. (1924), was charged that, being registered under the Medical Acts and having undertaken to provide general medical services under the National Health Service, on July 30, 1955, he failed without reasonable cause to visit and treat Anita Jane Beighton (aged 14 months) whose condition so required and for whose treatment he was responsible under the National Health Service, and that during a period between Feb. 27 and March 27, 1959, he failed without reasonable cause to visit and treat the late Mrs. Grace Annie Rose Spencer whose condition so required and for whose treatment he was responsible under the National Health Service. The charge continued: "By your conduct as aforesaid you neglected your duties as a medical practitioner under the National Health Service and disregarded your personal responsibilities to the patients whom you had accepted on your list, and that in relation to the facts alleged you have been guilty of infamous conduct in a professional respect". The committee determined that the facts alleged against Dr. Beith had been proved to their satisfaction. They considered these facts to be regrettable, but came to the conclusion that they did not constitute infamous conduct in a professional respect, and they recorded a finding that Dr. Beith was not guilty of infamous conduct in a professional respect.

CASES POSTPONED

In the absence of any evidence concerning the habits and conduct of FLORENCE BERCHMANS LAWLOR, registered as of 50, Beaumont Street, London, W.1, M.B. N.U.I. (1936), against whom judgment had been postponed for a year following convictions for being in charge of a motorcar when under the influence of drink in 1960 and unlawfully obtaining drugs by false pretences in 1959, the committee did not feel justified in discharging the case at present and therefore postponed judgment for a further six months, until May 1961.

The committee were not satisfied that the evidence produced on behalf of RICHARD MAURICE DOOLEY, registered as of 74, Eglinton Road, Donnybrook, Dublin, M.B. Dubl. (1945), would warrant them discharging the case at present. They therefore postponed judgment for a further six months on four convictions involving drink.

WILLIAM QUIRKE, registered as of Mountjoy Lodge, Kildare, L.R.C.P.I. (1949), was charged with having been convicted on

two charges of obtaining drugs by false pretences and one of unlawfully procuring dangerous drugs for which at the Castleford West Riding Magistrates' Court on June 1, 1960, he was fined £100. Judgment was postponed for a year.

ALFRED FRANCON WILLIAMS, registered as of 18, Crabtree Lane, Sheffield 5, M.B. Edin. (1940), was charged with having been convicted at Sheffield Magistrate's Court on July 19, 1960, of being drunk in a public place, when he was fined 10*s.* and ordered to pay 7*s.* 6*d.* costs, and of a like offence at the same court on Sept. 19, when he was fined £1. Judgment was postponed for a year.

HENRY JOSEPH CARON, registered as of The Surgery, Tyntyla Road, Llwynypia, Rhondda, Glam., L.A.H. Dubl. (1949), admitted a conviction at Ystrad Magistrates' Court on eight charges of unlawfully procuring dangerous drugs, for which he was fined £200 and ordered to pay £10 10*s.* costs. Judgment was postponed for one year.

CASES CLOSED

The committee determined that the Registrar should not be directed to erase the names of HENRY STANLEY MARSHALL PERERA, L.R.C.P.E. (1959), registered as of Daisy Hill Hospital, Newry, Co. Down; of GEOFFREY RODERICK RICHARDS, M.R.C.S. (1937), registered as of 5, Corrymore Mansions, Sketty Road, Swansea; and of GEORGE LEWIS MINTER, M.B. Edin. (1950), registered as of 133, Queen's Road, Blackburn, Lancashire. In each of these cases judgment had previously been postponed.

CASE HELD OVER

The case of LOH MUNG SUN, registered as of 25, Channel Road, Sibu, Sarawak, Borneo, L.R.C.P.E. (1917), was postponed to the next meeting of the committee.

Symposium

ANTICOAGULANT THERAPY

FROM A CORRESPONDENT

A SYMPOSIUM on Anticoagulant Therapy was held in London on Nov. 18 and 19.

Reviewing laboratory control, Dr. R. P. BIGGS (Oxford) said that the coumarin anticoagulant drugs cause a fall in the blood level of factors VIII, IX, and X, and of prothrombin, and influence the adhesiveness of platelets; factors V and VIII are unchanged. She suggested that the responsibility of the laboratory worker is primarily to ensure that the levels of these factors never fall so low as to cause hæmorrhage; in other words, he should prevent the clinician from allowing these drugs to degenerate into hæmorrhagic poisons. The one-stage prothrombin test is widely used; for, by and large, it distinguishes safe from unsafe levels of treatment. The drawbacks of this test are its insensitivity to small deviations from normal and the technical effect of different sources of tissue-extract on the results. The prothrombin and proconvertin method is more sensitive in the near normal range, but this test still requires carefully standardised reagents. The thrombotest method provides a standardised reagent and seems the most suitable for routine use in small laboratories.

In the past ten years Prof. P. A. OWREN (Oslo) has pioneered a large-scale and expanding programme of lifelong prophylactic anticoagulant therapy in Norway, and he introduced the thrombotest in response to the need for a simple and reliable test to subserve this programme under variable laboratory conditions throughout the country. Dr. W. WALKER (Dundee) has confirmed its value and recommends that capillary blood be obtained by a scalpel wound of the lateral aspect of a finger. The thrombotest method is apparently ideal for the control of anticoagulant therapy in, for instance, the small rural Australian communities with limited laboratory facilities described by Sir WILLIAM MORROW (Sydney). Long-term anticoagulant therapy would be extremely hazardous or even impossible under these circumstances but for well-organised flying-doctor services and the keen enthusiasm of country practitioners who contend with their own laboratory techniques.

Professor Owren's Norwegian programme of life-long anticoagulant therapy embraces rheumatic heart-disease with embolism, angina pectoris of less than two years' duration, myocardial infarction after the first attack, and thrombosing atherosclerosis of the legs and of the cerebral circulation. Support of the value of such a regime in myocardial ischæmia was forthcoming from Dr. A. S. DOUGLAS (Glasgow), who cited the results of the Medical Research Council's long-term anticoagulant trial; from Dr. M. M. SUZMAN (Johannesburg), who found that the fatality-rate fell from 54% to 22% with prolonged therapy; and from Dr. PAUL WOOD (London), who observed that the mortality among treated cases of coronary insufficiency is a fifth of that in the controls. Dr. Wood felt that patients repeat their pattern of onset of symptoms, and this provides some guidance in the selection of cases for long-term anticoagulant treatment. Patients in whom severe symptoms developed suddenly are liable to have this experience again without warning, so for these it seems advisable and safer to continue on long-term anticoagulants, whereas those in whom adequate warning is given by crescendo angina of effort can be controlled as symptoms arise. Dr. Wood suggested that all patients receiving anticoagulants should carry cards indicating the dosage and serial prothrombin-times. Dr. H. LEMPERT (Manchester) disagreed, for the introspective can be profoundly anxious over minor variations in these readings. Those who have endeavoured to console introspective rheumatoid patients over minor fluctuations in their erythrocyte-sedimentation rates will sympathise with Dr. Lempert's viewpoint. Most would agree with Dr. WOOD and with Prof. R. B. HUNTER (Dundee) that the ultimate responsibility for the control of treatment, although dictated by laboratory means, lies with the clinician.

Dr. DOUGLAS has questioned 30 doctors covering a population of 70,000 in the environs of Glasgow to assess the number of patients who had sustained one myocardial infarct or who had effort angina. From this survey, it seems likely that about 10% of the population would need long-term anticoagulants. Dr. M. F. OLIVER (Edinburgh) has calculated that such an incidence would cost the country £1 million annually. But Professor OWREN pointed out that this stressed the debit without taking into account the large credit side of lessened mortality and morbidity. Dr. Oliver supported this by citing worth-while expenditure of £6 million on poliomyelitis immunisation. Dr. J. L. STAFFORD estimated that the service costs £1 per patient's visit to St. George's Hospital, London, and Dr. STARK MURRAY that the domiciliary service in the Kingston area costs £1 per test.

Anticoagulant therapy is not free of danger. Dr. R. W. EMMANUEL (London) mentioned an increased risk of fatal hæmorrhage in Eisenmenger's syndrome and Dr. John MARSHALL has dealt with some instances of complicating cerebral hæmorrhage. Prof. SHEILA SHERLOCK (London) enjoined caution in its use in patients with liver disease. Failure of blood coagulation is a recognised complication of jaundice and hepatocellular dysfunction, and when congestive hepatomegaly develops in patietts receiving anticoagulant therapy their prothrombin-times may rise to alarming levels and hæmorrhage may ensue. Nonetheless, liver disease need be no bar to anticoagulant therapy so long as careful laboratory control of blood-clotting and of liver-cell function is maintained. She drew attention to the rarity of intravascular thrombosis and atherosclerosis in patients with chronic parenchymatous liver disease, and indicated that this observation may prove to be a growing-point in our better understanding of these phenomena. Although the cirrhotic may be spared the sequelæ of atherosclerosis and myocardial ischæmia this cannot be construed as a good argument for alcoholism.

The proceedings of this conference are to be published by Harvey & Blythe, Ltd.

In England Now

A Running Commentary by Peripatetic Correspondents

I SHALL never understand how a people who set as much store by comfort as do the Americans—with their big, well-sprung cars, centrally heated homes, and air-conditioned offices—can tolerate and even encourage shower-baths. In many places where they live there is either no tub at all or else one of such curious shape and meagre dimensions that it is all but impossible to use it in any position save the erect. I note that that great critic, Mr. Edmund Wilson, who claims that he has had more "uplifting thoughts, creative and expansive visions" in American bathrooms than in European cathedrals, speaks of "soaking in comfortable baths or drying myself after bracing showers". He does not pretend that showers are comfortable.

When you turn on a shower, nine times out of ten your arm must be in the line of the shower if you are to reach the tap. The initial unavoidable blast of cold water is not so bad; but if you have misjudged the proportions of hot and cold, your arm will be exposed to another cold blast, or else a scalding one, when it timidly reaches out to readjust the tap. This procedure often has to be repeated several times. It is usually possible to step into the shower backwards to avoid the flood on your face and eyes—though hazardous if the floor is as slippery as it is in nine showers out of ten. Some showers are almost large enough for you to bend over and wash your feet without striking your head on the wall. Some even have a receptacle for the soap; in the others you have to hold it in your hand all the time or keep retrieving it from the floor. In cold weather a tub will surround you with delicious warmth, like central heating; not so the shower. It is very difficult to get the water to run down your back and front simultaneously, and in general the effect is like that of the Old World's coal fire—you are comfortable (if not burned) on one side and frozen on the other. If the water is too cold, and you are foolhardy enough to try and adjust it, you will usually find that the hot-water tap is so sensitive that the least touch will cause it to eject a jet at scalding temperature. Worse; there may be temperature changes beyond your control—in the words of Vladimir Nabokov, showers have "one definitely neo-Laodicean characteristic in common, a propensity, while in use, to turn instantly beastly hot or blindingly cold on you, depending on whether your neighbour turned on his cold or his hot to deprive you of a necessary complement in the shower you had so carefully blended".

It is argued in favour of showers, first, that they use up less of the community's water than a tub bath—an assertion that I disproved by taking a shower in a tub with the plughole plugged and finding the water near to overflowing long before I had finished; and second, that you get cleaner than you would in a tub, sitting in water that gets dirtier and dirtier. There may be some truth in this, if you are really dirty—after, say, shovelling a couple of tons of coal from one bunker into another; but then not many Americans are often in this predicament. If, however, they come to realise how close in comfort coal fires are to their beloved showers, perhaps more of them will be.

* * *

Some years ago, when we were working with rabbits, we injudiciously bought a pair of electric clippers to facilitate cutting their hair. This apparently put us on the mailing-list of all the hairdressers' suppliers in Britain, and we have been bombarded and even pursued abroad by letters containing special Easter offers to trade in our worn-out scissors or telling us how to get another 3*d*. or 6*d*. on every haircut without having to spend any money on extra equipment or supplies. We have been offered large plastic stimulators and small rubber vibrators. "Bring more money into the saloon!" the postcards cry. Now that our local hairdressers' charges have gone up for the third time in two years, we are seriously thinking of trying it out. We have for some time been trimming the hair of our children with the rabbit clippers, and have acquired some small skill. In fact, last week we trimmed our rather shaggy cocker spaniel to perfection. It is only a question of changing over to bigger game, and we have offered, for half the official price, to cut the hair of our new graduate assistant in a saloon we have established off the feed-room in the animal house.

* * *

I now have no doubt that a country cottage is the best antidote to a consultant's life in a large industrial city. Stepping over the threshold seems to induce relaxation.

It isn't like the Ritz; and indeed the farm worker viewed it as unfit for human habitation and says that he's happier in the modern bungalow which has been built for him. With this excuse we have eagerly seized the cottage, and put it into good shape, mainly with our own hands. It is timbered, black and white, and built about 1640, and the presence of electricity enables us to rough it with electric blankets and other comforts when necessary. So far only one thing has marred it. The mental tranquillity of the Sunday has sometimes been replaced on the Monday morning, during Outpatients, by a humiliating looseness of the bowels.

I had thought of consulting a psychiatrist, as it seemed an obvious escape mechanism, symbolising an unconscious desire to rid myself of the humdrum of routine work. But serious consideration will now have to be given to an alternative diagnosis. I've just discovered that there is a dead horse in our water-supply.

* * *

Driving home on my weekend off, I was stopped by a herd of cows. After ten minutes of stopping and starting I began to infiltrate. The occupants of two cars going the opposite way looked at me rather oddly and one shouted something which sounded rude, but was unfortunately unintelligible. I stopped to allow a large bull to move out of the way and then started again. The car jolted, shook, and stalled. A large pothole, I thought—strange I hadn't noticed it. I started again, using the accelerator more strongly; the car rocked violently and stalled again. It had never behaved like this before; it felt alive. At that moment a soldier in an army truck climbed down and came to my window. "Excuse me, miss," he said, "but did you know—er, can I help you—you have a cow in your back bumper."

* * *

In the course of moving house in a northern purse-sparing community, I had to throw out a cupboard-full of old and more or less mutilated medical journals. My wife offered some samples to the local fishmonger. I am sorry to report that *The Lancet* came out of this test badly. "Nae, nae; the paper is o'er absorbent, and moreover the reading matter is too intellectual for most of my customers." However a stack of a sister journal was accepted with gratitude. "They'll do fine; good waterproof paper and plenty of interesting pictures; some in colour forbye."

* * *

The formal advertisement for an exchange of practices which you carry this week is the outcome of my dream of finding some way to get out of my routine life and to spend a sabbatical spell in some totally different environment. My practice is in rural Western North Dakota where there is grain-farming, ranching, oil drilling, and American Indians. The nearest large town is 70 miles away and the nearest hospital 32 miles. I have the rather large investment of a 5-bedroom home and an 8-room clinic (surgery) (X-ray, E.C.G., lab., &c.) with 3–8 year records on over 4500 people. Now there must be some doctor in Great Britain, like me, in his late thirties who is tied down with family and commitments and investments, who has had his nose to the grindstone since he left hospital work and his formal medical training, who has been seeing the same faces year in and year out until he wonders where it is all leading! Such a man I would like to step into my shoes, and I in turn would take over his practice. He could make my family and me very happy and at the same provide his own family and himself with an interesting opportunity for educational growth.

I wonder if I am your first peripatetic advertiser?

Letters to the Editor

"THEY NEVER TELL YOU ANYTHING . . ."

SIR,—"Of course, they never tell you anything in hospital" is, as Dr. Donaldson (Nov. 26) points out, a common remark of those who leave hospital, and is used by him and often by others, writing to the newspapers, as a stick to beat the hospital staff. Yet I think there are very good reasons why this statement, so often made, should not be taken at its face value, because I have long been interested in trying to find out exactly what it is that the patient has *not* been told. It is a most interesting aspect of the whole subject of doctor-patient communication, and considering how much the communication from patient to doctor (i.e., the evaluation of symptoms) is discussed it is odd how little attention is paid to the process in the opposite direction, the process of explanation, and how often it fails completely.

One finds this when one talks to patients after their return home from hospital. Most people are only too willing to talk of their operation, and while they often preface their remarks with "of course, they never tell you anything in hospital", it becomes obvious as they go on that, in fact, many people have taken great pains to tell them a lot. These patients certainly have no intention of telling a direct lie and would be horrified if they thought their remarks implied adverse criticism: they are generally grateful and "of course, the doctors and nurses were all marvellous". These same people with equal innocence often attribute to me, or my partners, remarks which we never made, and it must be familiar to all of us to hear with horror and wonder the things we are supposed to have said; that meningitis is due to thinking too hard, that someone is thin because threadworms eat up all their food, or that if the swelling of the ankles spreads up to the body the heart will stop. All these remarks have been attributed—incorrectly, I may say—to myself, and by patients who bear no antagonism and have no wish to slander me. This is just another example of failure of communication.

This failure arises chiefly, I believe, from failing to realise exactly how difficult the process of communication is, and that to most patients the simplest fundamentals of anatomy and pathology are as obscure as the fundamentals of an electronic computer are to me. It is not a question of intelligence, but of familiarity, and our constant day-to-day preoccupation with medicine dulls our appreciation of the obscurity of that diagram of gallbladder and common bileduct which we draw to explain to our patient his pain and his jaundice. Try and imagine a technician drawing a diagram to explain why your electronic computer can't add two and two when you don't even know what an electronic cell is.

This is only one aspect of the subject. Failure to discover and deal with hidden fears is another. Even more important perhaps, we may forget how much of hospital routine we take for granted—the intravenous drip, the tube up the nose, starvation before operation, the white sheet on the abdomen that must not be touched, pubic shaving, the first sight of a gleaming Boyle's machine, the unannounced technician with a 10 ml. syringe, the groans of the chap in the next bed, just back from theatre who sounds as if he is in agony even if he isn't. Very often the "anything" that "they never tell you" is the routine happenings of the ward, because to the staff it is ordinary common or garden *dull* routine—routine to the staff but a new and potentially terrifying series of experiences to the patient.

Finally there is the positive desire not to understand, in order to preserve at all costs the magic of the hospital so that it can work miracles if miracles are necessary. This most certainly exists, though it is too large a subject to expand on here. It is common in the elderly and it does explain why the remark "they never tell you anything" is so often voiced, not as a grumble, but with positive pleasure and as a mark of gratitude for services rendered.

Thus there are good reasons for believing in the first place that the remark "of course they never tell you anything in hospital" is just not true in its literal sense, and in the second place that simple measures like allotting to student, houseman, or registrar the job of "telling the patient, in simple lay terms" will do little to overcome the frequency with which the remark is heard.

Wantage, Berks. I. S. L. LOUDON.

SIR,—Dr. Donaldson oversimplifies the problem of telling patients about their illnesses when he says "someone" should tell "every patient" before leaving hospital what is wrong with them. He is dogmatic in implying that this is necessarily an important part of their treatment; and, I suggest, misguided if, in this context, he agrees with Emerson that "knowledge is the antidote to fear".

Like many housemen, I have been that "somebody" for a year now. I regard explanation to patients as, in large part, the houseman's responsibility and have tried conscientiously to deal with the problem, but I don't think I have evolved any satisfactory method.

Even with non-malignant disease it is far from easy. While agreeing with Dr. Donaldson that, too often, a patient is given inadequate information, it is remarkably difficult to explain to a layman anything except the simplest of diseases. On many occasions the consultant, the registrar, and I have given careful explanations to patients, only to find by the questions asked later that virtually nothing has been grasped of what has been said.

Malignant disease presents an even more difficult problem. Some patients undoubtedly wish to know what is wrong with them no matter what the implication. Personally, I think this a comparatively small proportion; but they should be told. Others show by their discussion both with doctors and nurses, or by their avoidance of discussion, or refusal to face up to manifest evidence of physical deterioration, that they do not want to be told anything. I have seen the personalities of such patients disintegrate at having unwanted explanation thrust upon them. Others purport to want to know, but, by the way they word their questions, do not want the truth. How else can one interpret the question: "I haven't got cancer, have I doctor?" Is the correct reply to this "yes"—however circumlocuted? It is simply not true, in my experience, that "very seldom will a 'white lie' have to be told" to a patient. It is necessary quite often.

Telling patients about their illnesses is not something that can be managed by any rule-of-thumb. Human beings must be judged individually. According to the ability of the doctor to do this astutely, so will he be able to decide on the form of explanation suited to each patient.

London, W.1. SIDNEY CROWN.

DRUG DOSAGE FOR INFANTS

SIR,—Your annotation of Oct. 29 drew attention to a formula based on surface-area. The method, which involved the calculation of the 0·7 power of the weight in kilogrammes, was said to be "both convenient and accurate". Before we all rush for logarithm tables and slide-rules, it would be as well to examine these claims.

The convenience of a method is always a matter of opinion. I venture to suggest that the use of a nomogram has much to commend it. (Incidentally, poor mathematician that I am, to

my humble reckoning (kg.) $^{0.7}$ consistently comes out to 10 times the right figure. As regards accuracy, this raises several important issues. What degree of accuracy is necessary when prescribing for children? Is the danger one of giving too much or too little? Does it matter, for instance, if a child with a surface area of 0·4 m² (18 lb.) is administered the dose appropriate for a 0·5 m² (24 lb.)? Ought we to correct for the fact that average household teaspoon holds 1 ml. more than the apothecary's? Should we insist that amounts left on the spoon, in the glass, and down the bib are accurately measured and replaced?

Most pædiatricians will concede that such accuracy is unnecessary. Children have a generous margin of tolerance to drugs. Most three-year-olds tolerate, and indeed need, adult doses (e.g., antibiotics, anti-histamines, steroids, vitamins) and some require even more. A six-year-old 0·8 m² enuretic may sleep heavily on 20 mg. of amphetamine, whereas the average adult lies awake on a quarter of this dose. The 0·25 m² baby and the 2·5 m² adult are sedated by the same dose of phenobarbitone. Even with drugs to which infants are particularly susceptible (e.g., morphine, aspirin, iron) a 20% error either way will probably have little ill-effect.

There can be no substitute for experience in prescribing an effective and safe dose of a particular drug for a particular child with a particular disease. Much as I condemn formulæ for this purpose, my solution to the problem of the new or doubtful drug is to regard the adult dose appropriate for 100 lb. and to extrapolate accordingly—a method which shows surprising approximation to the surface-area scale and engenders the comfortable feeling that the amount administered will be safe if not effective.

Students are still taught one or more of the many formulæ devised for the calculation of drug dosage for infants and children. Their multiplicity is good evidence that none is satisfactory. The addition of yet another formula cannot detract from the wide variations of children in their reaction to drugs as compared with adults. The only answer is never to be far from a comprehensive set of dosage tables. There can be no such thing as a satisfactory formula.

London, S.E.1. HERBERT BARRIE.

CANCER OF THE ŒSOPHAGUS

SIR,—I was interested in the article by Mr. Greening and Mr. Ramsay (Nov. 19), and I should like to support their contention that an indwelling tube left in the œsophagus to traverse a malignant structure, in inoperable cases, should be of the largest possible bore so that the patient can swallow semi-solid food rather than fluids only.

I cannot help thinking, however, that the tube and apparatus which they described, and illustrated, is unnecessarily complicated, when there is, in general use, the excellent Mousseau-Barbin tube which fulfils all their requirements. Furthermore, the fact that this tube is too large to go through the œsophagoscope does not mean that it cannot be inserted through the mouth, and I should like to describe the method which, of late, I have found to be simple and effective:

An œsophagoscope is passed, under general anæsthetic, and the site of the growth is noted accurately and the stricture dilated with bougies to the maximum size. A fairly small gum-elastic bougie, say size 8, is than passed through the stricture and left in position while the œsophagoscope is withdrawn. A Mousseau-Barbin tube is then cut short at such a point that when the funnel-shaped upper end is engaging with the top of the growth it is known that the cut lower end will be in the stomach (easily assessed with the knowledge of the site of the growth). The cut end should be clean and smooth. This prepared tube is then threaded over the inlying bougie and pushed down into the hypopharynx with the finger. A small œsophagoscope is then threaded over the bougie until its lower end engages within the funnel end of the tube. One then merely pushes the tube down with the œsophagoscope, and it is guided through the previously dilated stricture along the indwelling bougie. When the appropriate distance has been reached—and this can be read off on the graduations on the œsophagoscope—the instrument and the bougie are removed, leaving the Mousseau-Barbin tube in position.

Patients who cannot be treated this way are those in whom it is impossible to find a way through the growth with the initial bougie. As a rule this difficulty is only met when the growth is at the lower end of the œsophagus or the cardia, and in my experience a lot of these growths require an exploratory thoracotomy to demonstrate inoperability, and the tube can be inserted via a gastrostomy on these occasions.

Park Hospital,
Davyhulme, Urmston,
Manchester. JOHN DARK.

POSTPARTUM PRE-ECLAMPSIA

SIR,—I read with interest the article by Flight-Lieutenant McFadyen (Nov. 5) and Mr. Sophian's comments (Nov. 12). It is unfortunate that no description of the placenta was included, for I believe the placenta is the key to the cause of postpartum pre-eclampsia.

Separation of an infarcted placenta is likely to be less complete than that of a healthy placenta, because fragments of the fresh friable infarcts tend to break off. Unlike healthy placental tissue or membranes, whose retention in the uterus causes hæmorrhage or sepsis, red infarcts are partly proteolysed and so comparatively absorbable. When absorbed into the maternal circulation they constitute "foreign" stress-producing material, which is nephrotoxic and causes toxæmia—albuminuria, oliguria, renal ischæmia, and hypertension—or accentuates existing toxæmia, or leads to a recrudescence of toxæmia some days after the death of a fœtus retained in utero. The rate of their absorption depends on the pumping action of uterine contractions, and the intensity of the toxæmia that results is proportional to the uterine activity (and also to the quantity and condition of the infarct material retained in utero).

This explanation offers a different interpretation, but conforms with the statement of Mr. Sophian that "the contracting postpartum uterus provokes renal ischæmia". The contracting intrapartum uterus also does so. Ergometrine, too, increases uterine activity, accelerates absorption, and (as Flight-Lieutenant McFadyen mentioned) aggravates the toxæmia. The great increase in maternal cortocosteroids, correctly stated by Mr. Sophian to be a non-essential part of the pre-eclamptic reaction, is probably provoked by the entry of "foreign" placental products during and after labour, when the uterus is most active. The coexistence of red infarcts and albuminuria was observed many years ago by Young,[1] and absorption from them of nephrotoxic material seems a more reasonable explanation of toxæmia than uterine stretch.

Thus, although the incidence of eclampsia reaches its peak during the hours of labour (fully 30% of cases occurring then) when stretch and activity of the uterus are both at their height, severe toxæmia or eclampsia may accompany the birth of a small, very premature baby—when the uterus is active but has been little stretched—or it may follow the birth of a baby by fully a day or two, when the uterus is still active but has ceased to be tensely stretched.

Inability to explain postpartum toxæmia and eclampsia has been a major obstacle to the acceptance of previous theories about the cause of eclampsia. Various workers have named various factors as specific causes. My own nominee is trans-

1. Young, J. *Proc. R. Soc. Med.* 1914, **7**, 307.

placental hormones,[2] but I believe these are only one important factor. Toxæmia results from the interplay of various factors—extrinsic (diet), intrinsic (hypertensive, renal), hormonal, mechanical, and infective—which lead to vasospasm and infarction. I have described [3] the pre-infarct and post-infarct stages of toxæmia, and postpartum pre-eclampsia is, I believe, a normal part of the latter stage.

Reading. K. D. SALZMANN.

TUBERCULOSIS NOTIFICATION

SIR,—You quote (Nov. 5, p. 1036) from the Registrar General's commentary the official figure for tuberculosis notifications in 1949 as 50,000 and for 1958 as 30,000.

On paper this looks very good and in fact would be good if 1958 were a true figure. You have previously published from me evidence that when the number of attested (tuberculin-tested) cattle increased, human tuberculosis also increased, and this applies to both pulmonary and non-pulmonary tuberculosis.

On Oct. 1 this year the whole of Great Britain was declared free of cattle tuberculosis so that during 1949–58 eradication of cattle tuberculosis was in its final stages.

Also during this period I suspect that the official figure was not correct. I remember a report from Hampshire of pulmonary and non-pulmonary tuberculosis in the same house: neither case had been officially notified. I suggest these are not isolated cases.

My opportunity of finding such evidence in a smallish veterinary practice is limited, but I will hazard that if all the individuals with tuberculosis were enumerated the 30,000 would be very near 100,000.

High Wycombe, Bucks. L. PITCHER.

WORKING WIVES—AND THEIR CHILDREN

SIR,—I have almost completed a review of the subsequent careers of the Oxford women medical graduates, and the findings are somewhat disturbing. 75 of the 93 women, who graduated between 1941 and 1950, have married. Of these 75 married women, 32 (43%) are practising between half and full time; 15 (20%) are practising less, and usually much less than half-time and the majority of these are anxious to spend more time in medicine; 6 (8%) are not practising and have no desire to resume, while 22 (29%) are not practising but are very anxious so to do on a part-time basis.

Accordingly about half of these married women seek, but are unable, to continue the career for which they trained. It would take too long to set out all the factors which cause this situation, and although it is true that lack of domestic help, income-tax laws, and the husband's occupation all play their part, yet the principal factor is the unwillingness of hospital authorities, medical officers of health, and general practitioners, to accept women in half-time posts. Unless the Ministry of Health can induce a change of heart on this point, it would be wiser, from the point of view of the nation's economy, if the admission of women to medicine were severely restricted, as the male wastage is so much less. On the other hand, they arrange things better in many European countries, where married medical women have no difficulty in obtaining satisfactory posts on a part-time basis.

The situation with regard to those who graduated prior to 1940 is rather different as a far higher proportion have remained single, for as one of them wrote " my generation of medical women were brought up neither to receive nor expect to receive any special consideration because we were women. The present generation takes it for granted that medical practice can be arranged around the life domestic ".

My advice, based on this study, to the woman medical student who wished to combine medical practice and matrimony would be a variant of that given by the oracle of Bouverie Street, " Don't get married until you have established yourself in medicine, marry a doctor and obtain long leave, but don't resign your post while having a baby, and thereafter only work half to three-quarters time; alternatively go abroad to a country (there are several) where domestic help is plentiful ". But Cupid is notoriously deaf to sage advice.

The Radcliffe Infirmary, Oxford. A. H. T. ROBB-SMITH.

MODERN CLINICAL BIOCHEMISTRY

SIR,—As head of a department which produces biochemists I should like to comment on the recent letters by Dr. Hendry (Oct. 29, Nov. 19), Dr. Woolf (Nov. 12), and others.

At the present time the demand for biochemists with science degrees greatly exceeds the supply. Of the various possible sources of employment the National Health Service offers a reasonably good financial inducement to the young scientist, but in my experience it is exceedingly difficult to persuade science graduates to accept posts in hospital biochemical laboratories. One of the things which deters them from entering the hospital service is the feeling that they will be regarded by their medical colleagues not as professional scientists and university graduates but rather as subordinates in the intellectual, economic, social, and professional category of technicians and medical auxiliaries. That these fears are not without justification is very beautifully illustrated in the unfortunate letter of Dr. Osborn (Nov. 5). It is true that science graduates express fewer misgivings about entering the biochemical laboratory of a large teaching hospital where they are under the control of a professional biochemist as head of a department, but it is becoming increasingly difficult to persuade them to work in the smaller hospitals where all the laboratory services are grouped under a non-biochemical pathologist.

One disturbing result of this attitude is that the best science graduates tend to shun hospital employment—it is very rare for a first-class honours man to enter a hospital laboratory. The consequent flow of a number of the less able graduates to the hospitals is apt to give the medical staff a less favourable impression of the usefulness of scientists in their midst than they might otherwise gain. And so the vicious cycle begins.

There is no doubt that the best training for a hospital biochemist is an honours science degree in biochemistry supplemented by a medical qualification; but such a training is lengthy and only a few students (about two per year in Glasgow) are willing to face it. The basis of the biochemist's training must be *chemical* whereas that of the pathologist must be *medical*, but the biochemist at the end of his training must be able to discuss problems of mutual interest for the patient's welfare with his pathological colleagues as an equal and not as a subordinate and he must have direct access to the clinician in charge of the patient. This is not merely a matter of professional pride—it is the only way to encourage the ablest biochemists to enter, and to remain in, hospital work.

It may be administratively untidy to have the biochemical laboratory of a hospital separate from the pathological laboratory which covers morbid anatomy, bacterio-

2. Salzmann, K. D. *Lancet*, 1955, ii, 953.
3. Salzmann, K. D. Aetiology and Arrest of Pre-eclamptic Toxæmia with Early Ambulant Treatment. London, 1960.

logy, and hæmatology, but it is becoming more and more obvious that such an arrangement is essential for the good of the patient in any large up-to-date hospital which expects good service from a competent staff. In those hospitals where this system operates, the results amply reveal its justification.

Department of Biochemistry, University of Glasgow. J. N. DAVIDSON.

HYALINE MEMBRANE FOLLOWING TOTAL BODY RADIATION

SIR,—According to the preliminary communication in *The Lancet* of Nov. 5, patients with far-advanced malignancies have been subjected to total body irradiation for an experimental purpose, and one not related to their disease.

The effects of such irradiation are severe, and, at the dosage mentioned, lethal.

I think these circumstances ought to be remarked, particularly as you ignore them in your editorial comment.

Manchester. J. L. DOBBIE.

*** We showed Dr. Dobbie's letter to Captain King and his colleagues and their reply follows.—ED. L.

SIR,—We should like to make the following points and perhaps clear up this misunderstanding:

(1) Except for one (who had a kidney transplant) all patients selected for this form of therapy had disseminated malignancies. Conventional therapy had failed in these patients and localised radiation therapy revealed some degree of radiosensitivity.

(2) The observations on human lung were incidental to and not the purpose of the therapy.

(3) As you will note, the operative mechanisms of plasmin inhibition following total body radiation were worked out in dogs, not humans.

(4) As a result of extensive investigations on the subject of total body radiation in animals, the serious effects in the unsupported subject are well appreciated at the National Naval Medical Center, Bethesda.

(5) The efficacy of total body radiation will be presented in detail in a future publication.

WILLIAM H. FLEMING
JENO E. SZAKACS
THOMAS C. HARTNEY
E. R. KING.

U.S. Naval Hospital, Bethesda, Maryland.

SUICIDE

SIR,—The changes in the law of suicide foreshadowed by a report from the Criminal Law Revision Committee [1] will be welcomed by doctors, magistrates, and police officers alike. It has long been recognised that the existing law has no deterrent effect and creates a great deal of distress. Frequently it makes treatment more difficult by causing patients to deny suicidal intentions for fear of prosecution. Bringing a person who has attempted suicide before a court and placing him on probation under the condition that he receives psychiatric treatment is quite unnecessary. There is no reason whatever why England alone of all countries in the world should require special legal provisions, outside the mental-health legislation, to make people in distress accept medical and social help. As Dr. Casson (Nov. 5) referred to my studies on attempted suicide, or rather to a brief second-hand report of my studies, I wish to state that my observations [2 3] lend strong support to those who have for a long time advocated the abolition of the existing law. Its background and its effects were fully discussed three years ago.[4] On that occasion Batchelor reported on the way the problem is dealt with in Scotland where suicide and attempted suicide are not criminal offences.

Dr. Ahrenfeldt's letter (Nov. 19) about the attitude of the Church to suicide contains no reference to the recent report by a committee set up at the suggestion of the Archbishop of Canterbury for the purpose of examining the law of suicide.[5] The first of the four recommendations made by this committee was that attempted suicide should cease to be a criminal offence.

The University, Sheffield. E. STENGEL.

1. Criminal Law Revision Committee: second report (Suicide). H.M. Stationery Office, 1960. See *Lancet*, Oct. 29, 1960, p. 976.
2. Stengel, E., Cook, N. G. Attempted Suicide. London, 1958.
3. Stengel, E. *Medico-legal J.* 1959, **27**, 114.
4. *Proc. R. Soc. Med.* 1958, **51**, 297.
5. Ought Suicide to Be a Crime? Church Information Office, Westminster, 1959.

CIGARETTES IN HOSPITALS

SIR,—Some hospitals issue pamphlets about the risks of cigarette smoking, and many of their doctors, even if they can't stop the habit themselves, advise patients not to start. Is it not time that these hospitals reversed their illogical decisions to provide cigarette vending machines?

Enfield, Middlesex. C. ALLAN BIRCH.

ADMINISTRATION IN MENTAL HOSPITALS

SIR,—The Mental Health Act makes it quite clear that the responsible medical officer is not responsible or answerable for the patient's treatment to any other doctor. Therefore, in answer to Dr. Falla (Nov. 12), I would say that I do not need to know anything about those patients which are not directly under my personal care. Hypothetical cases make bad laws, but it follows from what has been said that, as medical superintendent, I would know nothing about the aggressive psychopath mentioned, and therefore the consultant, and he alone, would be called upon to give an explanation of the action of his patient.

I would, indeed, say that treatment includes control of freedom, prescription of social and occupational activities, the amount of pocket-money that a patient is allowed, and many other similar things, but that the actual prescription of these things will vary from patient to patient according to the judgment of the responsible medical officer. Nevertheless the medical superintendent being responsible for the efficiency of the whole hospital, and not only for the efficiency of his own team, has to see that these things are available for "prescription". Also he is responsible for coordinating and controlling new ideas and requests coming from the teams so that chaos does not ensue. It is also his job to see that all suggestions for improvement in the clothing of patients, the standard of catering, furnishing, and architectural improvement, lengthening of visiting hours, or anything else that is agreed upon at the weekly senior-staff meetings are carried out for the benefit of all the teams. All the new ideas coming out of the senior-staff meeting will then be put into practice satisfactorily throughout the hospital and implemented after any necessary consultation between the medical superintendent, chief male nurse, matron, and hospital secretary.

I think this really answers Dr. Bardon (Nov. 12), for it will be seen that a medical superintendent responsible for the efficiency of the whole hospital does not in anyway impair the freedom of the clinical teams. In any event, Dr. Bardon has misread the Act. The Act has nothing to say, either specifically or implicitly about how a hospital is adminstered. His idea of an elected chairman might well work and become the pattern of the future, as I suggested in my first letter. But in my view most mental hospitals at present still need a

medical superintendent who directs the hospital as a whole and who has powers, not to interfere in any way with the treatment of a patient, but to interfere in matters of administration and discipline of medical and nursing staff if, in his opinion, their action might be seriously detrimental to the harmony of the hospital. For such decisions he should be answerable to the hospital management committee or the regional hospital board who appoint him and not to his colleagues.

Evolution is much better than revolution and my feeling is that Dr. Bardon and many clinical psychiatrists express their views so radically and so forcibly that I suspect that powerful unconscious motives may be at work. Finally we should not slavishly follow the general-hospital pattern of administration. It too has its faults.

The Towers Hospital, Humberstone, Leicester. H. B. KIDD.

PROGNOSIS AND ANTICOAGULANT PROPHYLAXIS AFTER CORONARY OCCLUSION

SIR,—Like Dr. Byron Evans (Nov. 26), many of us are grateful to Professor McMichael and Dr. Parry (Nov. 5) for questioning the value of long-term anticoagulant prophylaxis after cardiac infarction. It is dangerous, and cannot but be tedious except for a hypochondriac.

It would be a pity, however, if there were a premature reaction, provoked by annoyance with opinionated but inadequately informed patients, against its use in the first few weeks after an infarction. Many observers believe its use in this period to be vitally important.

We are thankful for iconoclasts like Dr. Byron Evans. If too inflexible, however, they are in danger of getting cut off by the tide of progress.

Barton-on-Humber, Lincs. S. H. F. HOWARD.

SHINGLES AND CHICKENPOX

SIR,—I think the following case shows that the relationship between these conditions is not necessarily indirect, as Dr. Ball (Nov. 19) suggests, and that an intermediate host may not be required.

A young woman was admitted under my care in 1955 to the British Military Hospital at Rinteln, B.A.O.R., with herpes zoster of the ophthalmic division of the left trigeminal nerve, causing severe conjunctivitis and keratitis. Because her husband was away on a military exercise, she was admitted with her infant aged six months. Fourteen days later, the baby developed chickenpox, and I think it reasonable to assume that contact here was direct, since they were nursed in an isolation ward.

Military Hospital, Colchester. H. FOSTER.

RESPIRATORY OBSTRUCTION DUE TO FAULTY ENDOTRACHEAL TUBE

SIR,—I was interested to read the article of Oct. 1 by Dr. Pryer and his colleagues. I have twice encountered the accident they describe, and I think it is important that it should be mentioned in the textbooks. The story in the two instances I mention was the same—a sudden onset of complete obstruction in a previously uneventful anæsthetic. Fortunately in both cases I was called before a fatal outcome, and by deflating the cuff completely, relieved the situation. When the tubes were examined subsequently, it was found that there was a " hernia " in the cuff on the side opposite the side of the bevel.

When I am teaching I always include this among the complications of endotracheal intubation. I think that too small a tube, and overinflation of the cuff are the precipitating causes, and if the tube is appropriately chosen and the cuff just adequately inflated, this accident should not occur.

Brisbane Hospital, Brisbane. RUTH MOLPHY.

CHEST X-RAYS AND RADIATION HAZARDS

SIR,—I write in complete agreement with Dr. Beresford's letter of Nov. 26. I should like to enlarge upon his condemnation of fluoroscopy sessions as a means of diagnosing early pulmonary tuberculosis. This method is still adopted at certain clinics in preference to a chest X-ray. I have long felt that fluoroscopy for this purpose is entirely unjustified, not only, as Dr. Beresford points out, because the amount of radiation at each examination is substantially greater than the controlled dose given by radiography, but because there is no permanent record which could be of great assistance later. Furthermore, I have tested the method myself by screening a few patients whose chest X-rays showed a minimal tuberculous lesion and found that, even after adequate accommodation to the darkness (my day and night vision is perfect), I was quite unable to detect these lesions on fluoroscopy. And, of course, I did know where to look, having first seen the chest X-ray.

Bow Arrow Hospital, Dartford. M. O. J. GIBSON.

HYPERSENSITIVITY TO MILK AND SUDDEN DEATH IN INFANCY

SIR,—The team of workers who have produced, in your issue of Nov. 19, such a convincing solution to the mystery of sudden cot-death in infants are to be congratulated. That these tragic deaths may result from the aspiration of cow's milk during sleep in a child who is already sensitised to the protein in the milk is, as they emphasise, a valid reason for encouraging breast-feeding wherever possible. Those of us who still believe that breast milk is the only proper food for the healthy baby will be glad to have such strong support for our beliefs at a time when so much is written in defence of artificial feeding.

Inevitably there will be occasions when breast-feeding is impossible, and then we must be especially careful to guard against the danger of aspiration of feeds.

In the past, in my opinion, far too much stress has been put upon the dangers of suffocation. This is perhaps the reason why the nursing of infants in the prone or semi-prone position has not been more widely practised. Provided the baby lies upon a firm mattress *without* a pillow, his nose-clearing reflex ensures that his head is always turned to one side. Lying in this position regurgitation becomes almost impossible, and, if it should occur, the milk is possetted harmlessly upon the sheet.

Premature babies regurgitate more easily than full-term infants, and some experienced nurses have learned to overcome this tendency by nursing them in the prone position. And the radiologist can demonstrate that the one position in which the infant cannot regurgitate an opaque meal is semi-prone on his right side.

Incidentally, this is a much more effective way of posturing the infant with cardiochalasia or hiatus hernia, particularly if the infant is tilted by raising the head of the cot on 18-inch blocks.

London, N.W.3. R. J. K. BROWN.

SIR,—Using the guineapig, an animal well known to be peculiarly immunologically fragile, Dr. Camps and his colleagues (Nov. 19) have nevertheless demonstrated as close an analogous pathogenetic explanation of the " cot-death syndrome " in infants as we are ever likely to

get. The fact that most infants fed on cow's milk develop antibodies to the proteins of that milk is proffered as another inducement to breast-feed young babies wherever practicable.

Is it then true, as would seem to be implied, that infants fed their mother's milk do not develop antibodies to human milk proteins?

Group Pathological Laboratory,
Royal Hampshire County Hospital,
Winchester. T. J. MUCKLE.

POSSIBLE SITE OF BIOCHEMICAL ERROR IN GAUCHER'S DISEASE

SIR,—Gaucher's disease, a familial disorder of lipid metabolism, results in the accumulation of a cerebroside in the cells of the reticuloendothelial system. This cerebroside is composed of a long-chain fatty-acid attached to sphingosine with an acid amide link. Galactose is attached to the end of the sphingosine with a glycoside link. The cerebroside is called kerasin if its fatty-acid is lignoceric acid, although other fatty-acids can be present. In some cases of Gaucher's disease, an abnormal kerasin has been found with glucose in place of the usual galactose portion of the molecule. In other cases the normal galactose cerebroside accumulates.

On the assumption that an enzymatic defect in cerebroside metabolism is responsible for the accumulation of cerebroside in Gaucher's disease, we have studied the incorporation of ^{14}C-labelled glucose and galactose into the microsome-supernatant fraction of a normal spleen and a spleen from a patient with Gaucher's disease according to the method of Burton et al.[1]

Spleens obtained at splenectomy of a boy with Gaucher's disease and from a normal boy with a ruptured spleen due to a sled accident were immediately frozen with dry ice-ethanol and stored at $-10°C$ in a deep-freeze until used. After homogenation of 4·8 g. of spleen with 20 ml. of 0·25 *M* sucrose, the microsome-supernatant fraction was separated by centrifugation in a Lourdes centrifuge at 0°C. A portion of the microsome-supernatant fraction was rapidly heated and maintained at 50°C for 2 minutes and then placed in an ice bath with the unheated portion until used. To each 0·9 ml. aliquot of the microsome-supernatant fraction was added 0·1 ml. $MgCl_2$ solution ($5·5 \times 10^{-3}$ *M*), 0·1 ml. adenosine triphosphate (A.T.P.) solution ($5·5 \times 10^{-3}$ *M*), 0·1 ml. uridine triphosphate (U.T.P.) solution ($5·5 \times 10^{-3}$ *M*) and either 0·1 ml. glucose-U-^{14}C (glucose uniformly labelled with ^{14}C) solution ($8·3 \times 10^{-4}$ *M*; 0·33 mC per mmole) or 0·1 ml. galactose-1-^{14}C ($1·1 \times 10^{-3}$ *M*; 0·25 mC per mmole).

After incubation at 37°C under a mixture of 95% N_2 and 5% CO_2 for two hours, 20 ml. of chloroform-methanol (2:1) was added to each vessel and brought to a boil to stop enzymatic activity. To each vessel was added 0·1 g. of crude cerebroside to facilitate extraction. The cerebrosides were isolated by passing the solution over a mixed-bed column of Dowex 1 and Dowex 50, layered with Florisil modified after Radin et al.[2] Each eluate was taken to dryness, dissolved in 10 ml. chloroform-methanol (2:1) and washed 5 times with 10 ml. of chloroform-saturated methanol water (1:1). Each precipitate was dissolved in chloroform-methanol (2:1) and evaporated in a warm water-bath to 1·5 ml., plated, and the radioactivity counted.

The mean incorporation of sugar in microsome-supernatant fraction (counts per min. per 100 mg. cerebroside ± S.E.) was:

	Glucose-U-^{14}C	*Galactose-1-^{14}C*
Normal spleen	34·6±5·5	36·7±16·9
Gaucher spleen (unheated)	100·9*±6·2	106·1*±5·3
Gaucher spleen (heated)	93·6†±3·7	213·7‡±14·4

* Differ significantly ($P<0·01$) from normal spleen.
† Differs significantly ($P<0·01$) from galactose incorporation (heated).
‡ Differs significantly ($P<0·01$) from galactose incorporation (unheated).

Both glucose and galactose were incorporated to a significantly greater extent in the Gaucher spleen cerebroside than in the normal. Heating resulted in no significant difference in the incorporation of glucose into Gaucher spleen cerebroside, but did result in a significantly greater incorporation of galactose.

From these results, we propose that the first step is the addition of glucose rather than galactose to the acceptor substance. It has been shown by others that the acceptor substance is sphingosine and that the fatty-acid is added after addition of the hexose. In turn, the glucose cerebroside is converted to galactose cerebroside through catalysis by a heat-sensitive epimerase enzyme. A defect in this epimerase enzyme in Gaucher's disease would result in the accumulation of the glucose cerebroside. An enzymatic defect in the catabolism of galactose cerebroside would explain those cases in which galactose cerebroside is found to accumulate.

This study was aided by U.S.P.H.S. grants A-2504 (c1) and 2G-346 (s1).

Department of Pediatrics,
State University of New York,
Upstate Medical Center,
Syracuse. MARVIN H. STEIN
LYTT I. GARDNER.

1. Burton, R. M., Sodd, M. A., Brady, R. O. *J. biol. Chem.* 1958, **233**, 1053.
2. Radin, N. S., Lavin, F. B., Brown, J. R. *ibid.* 1955, **217**, 789.

β-GLUCURONIDASE ACTIVITY OF CORONARY ATHEROSCLEROTIC PLAQUES

SIR,—In view of the present controversy about the pathogenesis of atherosclerotic lesions, increasing attention is now being given to the arterial intima and the intimal reactions in various types of atherosclerotic plaques. Our studies have included the examination of arterial lesions by the surface preparation technique,[1] tissue culture of arterial intima, and enzymological analyses of atherosclerotic plaques. It is the results of this third method which we report here.

In an analysis of coronary atherosclerosis with special reference to occlusive thrombi[2] it was also found that the fully developed atherosclerotic lesions could be divided into two distinct histological types:

(1) The crescent-shaped hard lesion composed of laminated layers of collagen and fibrin.

(2) An essentially fatty lesion composed almost entirely of sudanophilic material, separated from the circulating blood by a thin film of endothelium or fibrin.

Furthermore, transverse sections of coronary arteries from a large number of cases have shown that the earliest lesion in the development of atherosclerosis is the accumulation of acid mucopolysaccharide in the intima. Consequently in this enzymological investigation the plaques were classified in three groups:

(1) The active proliferative lesion—rich in acid mucopolysaccharide and showing various degrees of fibroblastic proliferation.

(2) The hard fibrocollagenous lesion.

(3) The fatty or soft plaque.

It was decided to estimate the β-glucuronidase activity in these three types of lesion because it has been suggested that β-glucuronidase plays an active role in cellular proliferation and tissue regeneration,[3] and as β-glucuronidase catalyses the hydrolysis of glucuronides it may play a part in the metabolism of glucuronic acid, a molecular constituent of the acid mucopolysaccharide of arterial intima.

The β-glucuronidase activity was therefore estimated in normal intima and in intima in the three main types of atherosclerotic lesion described above in 160 men and 160 women. The method was a modification of that given by Talalay et al.[4] and results are expressed as μg. of activity per g. of tissue per hour:

Type of arterial lesion (40 in each group)	*Mean β-glucuronidase activity (μg. per g. per hr.)*	
	Men	*Women*
Normal intima	30	50
Active proliferative lesion	700	840
Hard collagenous lesion	390	520
Soft or fatty lesion	200	290

These findings indicate:

(1) The active proliferative lesion, rich in ground substance and showing active fibroplasia, has the highest enzymic activity.

1. Lautsch, E. V., McMillan, G. G., Duff, G. L. *Lab. Invest.* 1953, **2**, 397.
2. Branwood, A. W., Montgomery, G. L. *Scot. med. J.* 1956, **1**, 367.
3. Levvy, G. A., Kerr, L. M. H., Campbell, J. G. *Biochem. J.* 1948, **42**, 462.
4. Talalay, P., Fishman, W. H., Huggins, C. *J. biol. Chem.* 1946, **166**, 757.

(2) This activity decreases as the plaques become more collagenous and less cellular.

(3) The accumulation of lipid to form the fatty plaques is associated with a marked reduction in enzyme activity.

(4) The mean enzymic activity of normal intima and of all plaques is higher in women than in men.

These results are largely confirmed by Dyrbye and Kirk,[5] who showed that the β-glucuronidase activity of normal coronary-artery intima had a mean value of 55 units. They did not comment, however, on any sex variation in the enzymic activity in their series of normal coronary-artery intima.

Department of Pathology, University of Aberdeen, Foresterhill, Aberdeen.

A. W. BRANWOOD
A. J. CARR.

5. Dyrbye, M., Kirk, J. E. *J. Gerontol.* 1956, **11**, 33.

Parliament

Medical Termination of Pregnancy Bill

Mr. KENNETH ROBINSON has introduced a Bill to amend the law relating to the termination of pregnancy by registered medical practitioners. It will be read a second time on Feb. 10.

QUESTION TIME

Hospital Staff Shortage

Lord STONHAM asked H.M. Government whether they were aware that in the North East Metropolitan regional hospitals the total staffs of physiotherapists are 32·7%, and psychiatric social workers 31·4% below establishment; that there was an almost equally acute shortage of radiographers, pharmacists, and almoners; that the position had greatly worsened since the beginning of the year, and what steps they would take to effect an improvement.—Lord NEWTON replied: The Government are aware that many hospital authorities find difficulty in filling their establishments for these classes of staff and that these difficulties are greater in some areas than in others. These professions are in competition with a number of other important professions, both inside and outside the National Health Service, and there are not enough young people of suitable calibre to fill all the available posts. For those whose training takes place in the National Health Service hospitals, recent figures of student recruitment are encouraging, and where specific difficulties, such as inadequate training facilities, hamper recruitment, the Government are prepared to consider how they can help. Salaries are a matter, in the first instance, for the appropriate National Health Service Whitley Council, but the salaries of all the classes mentioned have been substantially increased in the past two years.

Lord STONHAM: Is the noble Lord aware that despite the increased salaries which have been paid, the conditions are now disastrous; that the number of vacancies has increased since the beginning of last year by 50% in many cases and in some it has doubled, and that unless something very radical is done to bring about an improvement the hospital service is going to be seriously impaired?—Lord NEWTON: The noble Lord has great experience of these problems and he knows that it is the responsibility of hospital management committees to recruit their staff. But the Government are only too anxious to help in any way they can to solve these difficulties, and would welcome any suggestions. As I said in my earlier answer, the recruiting figures are now encouraging. I believe the reason for that is we are now beginning to see the results of the rise in the birth-rate which began in 1941. But it is true, of course, that the demand for these professions is expanding all the time as hospital facilities expand, and there is competition all the time for suitable people to fill these places.

Lord AMULREE: Although admittedly there has been some increase in salaries, does not the noble Lord think the salaries should possibly be made more commensurate with what these young girls can get in commerce?—The Earl of LUCAN: The noble Lord in his first answer mentioned training within the National Health Service and said the figures were now encouraging; but would he not agree that many of those who get their training in the health service afterwards leave for better-paid employment in industry?—Lord NEWTON: It is true that there is a good deal of wastage (to use a technical term), but I believe that this is largely because of marriage; and most of the members of these professions are, of course, women. All these five groups have received substantial salary increases within the past two years, and for none of them, at the moment, is a claim for a general pay increase before the appropriate Whitley Council. The trouble is that if, in due course, their salaries were increased substantially, those salaries would be met and matched by rises in the salaries of some of the other professions which compete for these people. Lord STONHAM: I am grateful to the noble Lord for his second answer to me and for the way he tried to meet the position, but I can assure him that the trouble is not marriage, it is salaries. I feel that the main obstacle is the fact that the Whitley Council machinery has virtually seized up.

Lord MCCORQUODALE OF NEWTON: I wonder whether I might suggest that part of the difficulty is the extension of the amount of knowledge that some of these people have to acquire before they get the appropriate degree or qualification, some of which knowledge is of not the slightest use to them afterwards. I am sure that less skilled procedure might lead us to more practical expertise in this matter.

Hospital Voluntary Funds

Dr. DONALD JOHNSON asked the Minister of Health what steps he was taking to encourage voluntary help in the raising of funds towards the financing of projects for new hospitals or new hospital departments.—Mr. ENOCH POWELL replied: It is my hope that all concerned with the development of the hospital service will not fail to make full use of contributions towards it which voluntary funds may offer. Dr. JOHNSON: Is the Minister aware of the general impression that voluntary funds for hospitals can be used only for purposes not directly connected with the running of the hospitals, such as patients' comforts? Will he take all possible steps to dispel this impression? Mr. POWELL: I hope that the question and my reply will help to do that. Dr. EDITH SUMMERSKILL: In view of the fact that successful voluntary effort depends on local circumstances, does not the Minister think that there should be some central supervision in order that all hospitals may be treated equitably? Mr. POWELL: What I have said is not inconsistent with the necessity for central supervision.

Representation of Consultants

Mr. L. A. PAVITT asked the Minister if he would give recognition to the council of the Regional Hospitals' Consultants and Specialists Association as being representative of the majority of consultants and specialists in the National Health Service; and if he would consult with the medical profession in order to secure a review of the constitution of the staff side of the Whitley Committee B to give a fairer balance between teaching and regional hospital representatives. Mr. POWELL: No, Sir. As regards the second part of the question, this is a matter for the staff side concerned. Mr. PAVITT: Is the Minister aware that 85% of the consultant specialists are working with regional hospitals, and not in teaching hospitals, and that 90% of the clinical work is being done by these consultant specialists in the regions? Why should not they have their proper place on all committees, including the Whitley Committee? Mr. POWELL: I am aware of the facts which the hon. Member mentions, but I am satisfied that the Joint Consultants' Committee adequately represents these consultants.

Treatment of Foreign Visitors

Mr. ALBERT EVANS asked the Minister if he would state the number of cases brought to his notice of foreigners entering, or attempting to enter, this country for the purpose of medical

treatment under the National Health Service. Mr. POWELL: In 1959, 1503 aliens were reported as entering, or attempting to enter, this country for medical treatment. 6 of these were refused entry. Steps were taken to ensure that the remainder paid for the treatment. Mr. EVANS: Will the Minister assure the House that in this matter he will follow the policy of all those Ministers who have held office since the inception of the National Health Service scheme? Will he refrain from looking at this matter from a narrow nationalistic point of view or with the idea of making petty economies? Mr. POWELL: This thing is an abuse. However relatively small the cost, it ought, so far as is practicable, to be prevented. There has been no difference in policy in this matter since the original Act.

Mr. MICHAEL FOOT: Is the Minister aware that when the service was first introduced the idea of giving treatment to sick foreigners was not regarded as an abuse but that we gloried in it? Mr. POWELL: There has never been any question of persons from abroad who fall sick in this country receiving attention under the National Health Service. That has not been in question from either side of the House. But it is not in accordance with the intention of the Act that aliens should come to this country for the purpose of getting treatment under the Act.

Remploy and the Mentally Disordered

Lord STONHAM asked H.M. Government if, in areas where suitable facilities were available, it would be possible for Remploy to act as agents for local health authorities in discharge of their responsibilities under the Mental Health Act, to provide training and occupation for the mentally disordered. —The Earl of DUNDEE, the Minister Without Portfolio, replied: My Lords, Remploy already provide employment for a number of mentally disordered persons. The company will continue to consider persons handicapped by mental disorders, together with other disabled persons for vacancies in Remploy factories, but it has no power to act as agents for local health authorities in the provision of training or occupation. Lord STONHAM: Is the noble Earl aware that my question invites consideration of granting such powers to Remploy? I would ask him to look at this matter again, particularly—having regard to the tremendous success of Remploy—with a view to seeing whether the Remploy sales organisation could not be used to dispose of the products of these centres, and in that way give the mentally disordered people a chance of earning at least part of their living instead of being in merely therapeutic centres. The Earl of DUNDEE: I am very grateful to the noble Lord for his appreciation of the excellent work which is being done by Remploy. They do employ, out of a total of 6300, I think about 500 people who are suffering from various kinds of mental or nervous disorders; and in view of the possibility of some of the persons placed by local authorities in special centres being able to go to Remploy afterwards very close touch is maintained. But that is not quite the same as giving the primary responsibility to Remploy for the care of mentally disordered people. Lord STONHAM: Is the noble Earl aware that what I have in mind is that in these local authority centres mentally disordered people will make something and it is absolutely essential that it should be sold by a skilled organisation; otherwise they will be at the mercy of charitable disposals and it will not be a really serious project. Would he consider that possibility? The Earl of DUNDEE: I gather the noble Lord is thinking of more efficient arrangements for the sale of their products, and I will most certainly look into that.

Poliomyelitis Vaccination

Poliomyelitis vaccine is now sufficiently plentiful to permit vaccination of those aged 40 and over who are not covered by the existing arrangements. From Jan. 1, family doctors will be able to vaccinate any such person who, they consider, requires this protection.

Children Remanded to Prison

During the nine months ended Sept. 30, 1960, in England and Wales, 585 boys and 23 girls under seventeen years were remanded to prison instead of being sent to remand homes.

Obituary

WALTER WEIR GALBRAITH

M.B. Glasg., F.R.F.P.S., F.R.C.S.E.

Mr. Walter Galbraith, consulting surgeon to the Western Infirmary, Glasgow, and a former president of the Royal Faculty of Physicians and Surgeons of Glasgow, died on Nov. 25 at the age of 71.

Born in Glasgow, he was the eldest son of the late W. B. Galbraith, J.P., C.A., and a brother of Lord Strathclyde. He was educated at Glasgow Academy and the Leys School, Cambridge. In 1914 he graduated M.B. from the University of Glasgow, and during the 1914-18 war he served overseas as a surgical specialist.

On demobilisation he was appointed to the staff of the Western Infirmary in Glasgow and rapidly earned a reputation as a gifted and courageous general surgeon. He early found his special interest in urology, and he was largely responsible for setting up a department of urology in the Western Infirmary.

He was also active in the affairs of his profession, his specialty, and his medical school. In 1949 he was president of the British Association of Urological Surgeons, and the following year he became president of the Royal Faculty of Physicians and Surgeons of Glasgow. At the time of his death he was a vice-president of the Royal College of Surgeons of Edinburgh. He was a member of the Scottish Health Services Council and for many years represented the Royal Faculty on the Joint Consultants' Committee and on the medical Whitley Council.

When he retired from practice in 1954 he made his home near Troon. There he found much pleasure in gardening and in the sports in which he excelled—golf, fishing, and shooting. Yet he accepted his leisure as an opportunity for further service. He continued as a member of the Joint Consultants' Committee, as a governor of Glasgow Academy, and as a director of the McAlpin Nursing Home, and he accepted two new charges in membership of the Western Regional Hospital Board and of the court of Glasgow University.

A. B. K. writes:

"Under Walter Galbraith's leadership the department of urology at the Western Infirmary made many contributions to the advance of surgery. Yet he will be remembered perhaps more for his generous personality which did so much to foster a happy relationship among the urological departments in the city. No visitor to his department was allowed to leave without being pressed to see the work of the others. He travelled extensively at home and abroad with urologists and with general surgeons. He revelled in companionship. His friendly interest strengthened many a younger man. His blunt but kindly criticism stimulated many a contemporary. His opinions were often based on emotion rather than on regulations. They were valued for their sincerity and humanity. To everything which he did he brought an unsurpassed gift for fellowship. He will be mourned by an innumerable company of friends."

S. A. pays tribute to him as a Scot as well as a surgeon:

"Walter's shrill and arresting 'What?' was like a pistol shot. It was the opening snap of cerebration. By the time the startled and discomfited colleague had filled diastole with a twice-told tale, Walter had formed an opinion—and a shrewd one at that. This idiosyncrasy epitomised much of his character. Essentially he was a man of business, a man of affairs, but schooled in the discipline of surgery; and in his chosen craft he was a master. His outward cheerfulness and boisterous

bonhomie were perhaps acquired in the interests of his friends. Behind this carefree style there was the astute brain of the relentless Scot—vigorous by disposition, yet able to carry the chains of convention and caution with relish rather than with dismay. The technical precision of the surgical specialist was complementary to the assiduousness of the committee-man. Purposive, tireless, and intensely patriotic, Scotland was his eyrie—and there he brooded like a golden eagle, jealously maintaining and defending the prestige of medicine in a changing world."

Mr. Galbraith is survived by his wife, a son, and two daughters.

Public Health

Foot-and-mouth Disease

THE present outbreak of foot-and-mouth disease [1] continues to spread despite all precautions. At midnight on Friday, Nov. 25, the Ministry of Agriculture announced that the movement of farm animals and the holding of markets was restricted in all counties of England north of a line from Bristol to London, with the exception of Cumberland and Westmorland. This widespread restriction was imposed because, during Friday, foot-and-mouth had been confirmed in Nottinghamshire, Essex, and Shropshire, and the outbreaks there could not be connected with any of the earlier cases.

By Monday, Nov. 28, a 9th case of foot-and-mouth disease had been confirmed in the Orkneys, bringing the number of outbreaks in Scotland to 66. The United Kingdom total was then 193. 3 more cases were confirmed during the day.

So far, the disease has not spread to Eire; but the Department of Agriculture in Dublin has asked farmers, cattle-buyers, and others who have any contact with livestock or meat in Britain not to visit Ireland until the present crisis is over.

There will be no livestock at this year's Smithfield Show, for the first time since 1798.

Up to Nov. 28, 14,700 cattle, 16,750 sheep, 6700 pigs, and 25 goats had been slaughtered.

Industrial Biological Research Association

A new research organisation—the British Industrial Biological Research Association—has been formed to study the possible effects on health, and to ensure the harmlessness, of substances which may be ingested in food, drink, and cosmetics. Supported by several leading companies, it is welcomed by interested Government departments and will receive a grant from the Department of Scientific and Industrial Research.

The Association's main object is the establishment of a biological research station for investigating the effect of substances used in food manufacture, either as processing aids for or flavouring and colouring food, as well as those which may get into food from pesticides, from plant used in food manufacture, from packaging materials, or from utensils. The Association hopes to build its laboratories at Leatherhead, Surrey, on land leased from the British Food Manufacturing Industries Research Association, which has offered to share some facilities and administrative services in the initial stages. The temporary headquarters of the Association are at 11, Green Street, London, W.1.

Classification of Occupations

Classification of Occupations [2] has been compiled by the General Register Office, England and Wales, and the General Registry Office, Scotland, primarily for use in the Census on April 23, 1961. It is also being used by the Registrars General for coding occupations stated at the registration of deaths and in morbidity surveys and inquiries. The *Classification* is published in the hope that it will be of interest to research-workers who may wish to relate their results to the Census statistics.

1. See *Lancet*, Nov. 26, 1960, p. 1183.
2. Classification of Occupations, 1960. H.M. Stationery Office. Pp. 136. 27*s*. 6*d*.

Diary of the Week

DEC. 4 TO 10

Sunday, 4th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
10.15 A.M. Mr. Wallace Black: Common Ear, Nose, and Throat Conditions.

Monday, 5th

UNIVERSITY COLLEGE LONDON, Gower Street, W.C.1
5.30 P.M. Prof. W. S. Feldberg: Mediators of Allergic Reactions.

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. J. F. Goodwin: Effect of Drugs on the Pulmonary Circulation.

Tuesday, 6th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1.
5.30 P.M. *Pathology*. Prof. N. F. Maclagan: Changing Views on Jaundice. (Presidential address.)
8.30 P.M. *Orthopædics*. Mr. Walpole Lewin, Mr. R. C. Connolly, Prof. Roland Barnes, Mr. F. C. Durbin: Injuries of the Head and Neck.

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. D. G. Catcheside: Functional Structure of Genes.

INSTITUTE OF OBSTETRICS AND GYNAECOLOGY
3 P.M. (Hammersmith Hospital, Ducane Road, W.12.) Mr. J. A. Stallworthy: Carcinoma of the Uterus.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright-Fleming Institute.) Mr. Aleck Bourne: Some of My Mistakes.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Mr. K. I. Nissen: Orthopædic Surgery of Spastic States.

ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Prof. F. A. R. Stammers: Pain in the Arm.

RESEARCH DEFENCE SOCIETY
5.30 P.M. (University College London, Gower Street, W.C.1.) Prof. J. H. Burn: Testing Drugs on Man. (Stephen Paget lecture.)

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Dr. Eliot Slater: Schizophrenic-like Psychoses of Epilepsy.

Wednesday, 7th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
2.30 P.M. Sir Stanford Cade: Malignant Melanoma. (Bradshaw lecture.)

ROYAL SOCIETY OF MEDICINE
5.15 P.M. *History of Medicine*. Mr. Dickson Wright: History of Opium.
8 P.M. *Surgery*. Mr. G. A. Mason, Mr. Charles Drew, Mr. A. J. Cokkinis, Mr. G. E. Mavor: Coronary and Mesenteric Vascular Occlusion.

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. A. E. Kellie: Steroid Assays.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. R. W. Riddell: Yeasts as Pathogens.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. Matthias Paneth: Surgery of Secundum Defects of the Atrial Septum.

INSTITUTE OF OBSTETRICS AND GYNAECOLOGY
2 P.M. (Queen Charlotte's Hospital, Goldhawk Road, W.6.) Mr. G. B. Gibson: Postmaturity.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Dr. Kenneth Soddy: World Mental Health Year—International Trends in Mental Health Work.

MIDLAND MEDICAL SOCIETY
8.30 P.M. (Birmingham Medical Institute, 36, Harborne Road, Birmingham, 15.) Dr. R. Bodley Scott: Acute Leukæmia—the Present Therapeutic Position.

Thursday, 8th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
3 P.M. Sir George Clark: Thomas Linacre. (Commemoration of the Quincentenary of Linacre's birth.)

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Mr H. J. Seddon: Manchester Ship Canal and Colonial Frontier. (Robert Jones lecture.)

UNIVERSITY COLLEGE LONDON
5.30 P.M. Sir Solly Zuckerman: Social Function of Science—1960. (Rickman Godlee lecture.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. E. J. L. Lowbury: Drug Resistance and the Response to Chemotherapy.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. P. F. Borrie: Disorders of Function in Cutaneous Blood Vessels and Lymphatics.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
4.30 P.M (Chelsea Hospital for Women, Dovehouse Street, S.W.3.) Miss J. A. M. Moore: Dysmenorrhœa.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place, W.1
7.30 P.M. Dr. S. Stott, Dr. E. van Oye, Dr. Henry Foy: Hookworm Diseases.

ALFRED ADLER MEDICAL SOCIETY
8 P.M. (11, Chandos Street, W.1.) Dr. Wilfred Barlow: Anxiety and Muscle Tension.

HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh.) Prof. M. L. Rosenheim: Small Kidney.

Friday, 9th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Dr. Victor Wynn: Metabolic Care of the Surgical Patient.
4 P.M. Dr. John Badenoch: Malabsorption Syndromes.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
3.30 P.M. Dr. Norman Hulbert: Headache and Facial Pain.

Notes and News

DOCTORS AND NATIONAL SERVICE

THE Minister of Labour stated in the House of Commons on Nov. 18 that men who had received enlistment notices instructing them to report to their units the previous day were the last to be called up and no further enlistment notices would be issued.

The Central Medical Recruitment Committees have already been able to meet the requirements of H.M. Forces for medical officers up to the end of this year. No further nominations to the Forces will be made, and any doctor who has not already been notified of his nomination to the Forces will not now be required for National Service.

Any doctor who wishes to consider a Regular commission in the Armed Forces should apply directly to the Service of his choice [Medical Director-General of the Navy (Admiralty), Queen Anne's Mansions, London, S.W.1; the Under Secretary of State, War Office (A.M.D. 2), Lansdowne House, Berkeley Square, W.1; the Under Secretary of State, Air Ministry (M.A.1), 1, Tavistock Square, W.C.1].

The principal task of the Central Medical Recruitment Committees has thus come to an end. During the period 1939–60, the committees recruited more than 27,000 doctors for service in H.M. Forces.

VISITORS FROM CHINA

REPRESENTING the Chinese Medical Association, six Chinese doctors are now visiting this country on the invitation of the Royal College of Physicians of London. The head of the delegation, Dr. Hsueh Kung-Chuo, is vice-president of the Chinese Academy of Medical Sciences, and the members are Prof. Chang Si-Chun and Prof. Liang Chih-Chuan of the Academy, Prof. Chu Ti-Tung and Dr. Lan Si-Chun of Shanghai, and Dr. Chu Shou-Ho of Peking. They are likely to be in Britain until Dec. 14.

HANDICAPPED CHILDREN

Princess Margaret, presiding at the 72nd annual general meeting of the Invalid Children's Aid Association, at St. James's Palace on Nov. 22, referred to a plan for a new school for "non-communicating" children, unable to speak because of profound emotional disturbance and specially studied by Dr. Louis Minski at Belmont Hospital. She said that about 9000 handicapped children had been helped last year, with 15,000 visits and interviews.

The annual report deals mainly with the Association's schools, and in moving its adoption Dr. A. White Franklin, the chairman, spoke of the need for money to finance new schoolrooms at the Meath Home, Ottershaw, at Pilgrims School, Seaford, and at Brentwood, St. Leonards. Pioneer work is being done at the John Horniman School, Worthing, for children needing residential intensive speech training from the age of 5. "Case work remains an important activity. The time has come for a combined case-work unit where the family could come in trouble and be helped as a family. A review of results should show whether case work is more effectively carried out by a general worker or by a specialist worker with a vocation such as for children, old people, or marital problems. Whatever the conclusion, workers and their parent associations would benefit from sharing work in a common centre."

The Earl of Feversham gave an address on Mental Health, describing the demands of life today, the scale and the cost of breakdown, and the mental makeup and basic needs of the individual. There are 200,000 people in mental and mental-deficiency hospitals (about half the hospital population), and one child in every twenty will need "mental treatment" some time in life. The only course at present is to help the individual to adjust to the environment, although research into physical and chemical influences on the brain is being carried out. In the presence of physical handicap, adjustment must include parents as well as child. The foundations of good family life are discipline, security, constancy, and a moral tradition arising from religion and background.

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued the following new supplementary list of approved names:

Approved name	*Other names*
Amphomycin	An antibiotic produced by *Streptomyces canus*
Betamethasone	9α-Fluoro-11β:17α:21-trihydroxy-16β-methylpregna-1 : 4-diene-3 : 20-dione 9α-Fluoro-16β-methylprednisolone
Biperiden	1-(*bicyclo*[2:2:1]Hept-5-en-2-yl)-1-phenyl-3-piperidinopropan-1-ol The name Akineton is applied to the hydrochloride and the lactate
Chlordantoin	5-(1-Ethylpentyl)-3-(trichloromethylthio)-hydantoin
Chlordiazepoxide	7-Chloro-2-methylamino-5-phenyl-3H-benzo-1:4-diazapine 4-oxide Librium is the hydrochloride
Chlorprothixene	α-2-Chloro-9-(3-dimethylaminopropylidene)-thiaxanthen Taractan
Chlorthalidone	3-(4-Chloro-3-sulphamoylphenyl)-3-hydroxy-*iso*indolin-1-one Hygroton
*Clonitazene	2-*p*-Chlorobenzyl-1-(2-diethylaminoethyl)-5-nitrobenzimidazole
Demecarium Bromide	Decamethylenebis(*m*-dimethylaminophenyl-*N*-methylcarbamate) dimethobromide Humorsol
Dioxamate	4-Carbamoyloxymethyl-2-methyl-2-nonyl-1:3-dioxolan
Ectylurea	α-Ethylcrotonylurea Nostyn
Ethchlorvynol	5-Chloro-3-ethylpent-1-en-4-yn-3-ol Placidyl
Ethosuximide	α-Ethyl-α-methylsuccinimide Zarontin
*Etonitazene	2-*p*-Ethoxybenzyl-1-(2-diethylaminoethyl)-5-nitrobenzimidazole
Hexapropymate	1-Propynyl*cyclo*hexyl carbamate Merinax
Hydromorphinol	14-Hydroxydihydromorphine
Isoaminile	4-Dimethylamino-2-*iso*propyl-2-phenyl-valeronitrile Dimyril is the citrate
Isoxsuprine	1-*p*-Hydroxyphenyl-2-(1-methyl-2-phenoxyethyl-amino)-1-propanol Dilavase is the hydrochloride
Methicillin	6-(2:6-Dimethoxybenzamido)penicillanic acid Celbenin is the sodium salt; Staphcillin is the sodium salt
Oxymetholone	2-Hydroxymethylene-17α-methyldihydro-testosterone Anapolon
Pemoline	2-Imino-5-phenyloxazolidin-4-one Kethamed; Pioxol
D-Penicillamine	(-)-ββ-Dimethylcysteine
Phenbutrazate	2-(3-Methyl-2-phenylmorpholino)ethyl α-phenylbutyrate
Phendimetrazine	(+)-3:4-Dimethyl-2-phenylmorpholine Plegine is the tartrate
*Phenoperidine	Ethyl 1-(3-hydroxy-3-phenylpropyl)-4-phenylpiperidine-4-carboxylate
Pipazethate	2-(2-Piperidinoethoxy)ethyl 10-thia-1:9-diaza-anthracene-9-carboxylate Selvigon is the hydrochloride
Plasminogen	The specific substance derived from human plasma which, when activated, has the property of lysing fibrin
Pyrazinamide	Pyrazinoic acid amide
Sodium Ironedetate	Iron chelate of the monosodium salt of ethylenediamine-*NNN'N'*-tetra-acetic acid Sytron
Streptodornase	An enzyme obtained from cultures of various strains of *Streptococcus hæmolyticus* and capable of catalysing the depolymerisation of polymerised deoxyribonucleoproteins
Streptokinase	A co-enzyme obtained from cultures of various strains of *Streptococcus hæmolyticus* and capable of changing plasminogen into plasmin
Tranylcypromine	(+) *trans*-2-Phenyl*cyclo*propylamine Parnate is the sulphate

* Narcotic substances which fall under international control and are not available as therapeutic agents.

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Proprietary name	*Approved name*	*Proprietary name*	*Approved name*
Akineton	Biperiden	Nostyn	Ectylurea
Anapolon	Oxymetholone	Parnate	Tranylcypromine
Celbenin	Methicillin	Pioxol	Pemoline
Dilavase	Isoxsuprine	Placidyl	Ethchlorvynol
Dimyril	Isoaminile	Plegine	Phendimetrazine
Humorsol	Demecarium Bromide	Selvigon	Pipazethate
Hygroton	Chlorthalidone	Staphcillin	Methicillin
Kethamed	Pemoline	Sytron	Sodium Ironedetate
Librium	Chlordiazepoxide	Taractan	Chlorprothixene
Merinax	Hexapropymate	Zarontin	Ethosuximide

CLINICAL RESEARCH LABORATORIES AT BIRMINGHAM

ON Nov. 15 Sir Henry Dale, chairman of the Wellcome Trust, opened the Wellcome Wing of Clinical Research at the Queen Elizabeth Hospital, Birmingham. The four-storeyed wing, which houses the laboratories for the whole-time clinical departments of the University of Birmingham, has cost £117,000. The Trust gave £95,000 for the building, and the University Grants Committee has provided the scientific equipment.

Surgery is housed in the top two storeys. The lower of these has a laboratory, 34 ft. by 50 ft. with bench-space and two screened-off portions with fume-cupboards; a small laboratory fitted for intestinal work; an office cum laboratory; and a seminar room to seat 50 people, fitted with projector services and a small library. On the top floor is an operating-theatre that will take all the monitoring apparatus necessary for experimental open-heart work, and can also accommodate four tables for simpler work. The sound-proof, plenum-ventilated and heated kennel-room will take 18 dogs, and there is a kitchen opposite for the preparation of their food. There are also two laboratories for isotope work, one with a fume-chamber, and a large electronics laboratory where at the moment work is being done on apparatus for open-heart surgery and cardiac arrest, and on inducted pace-makers for the treatment of Stokes-Adams disease, &c. There is also a technician's room.

Current research on the surgical side includes: the biochemistry of wound healing; hypersensitivity and auto-immunity as factors in non-specific intestinal granulomata; the reaction of the suprarenal cortex to surgical stress; portal and systemic venous levels of 5-hydroxytryptamine in intestinal disease; exfoliative cytology in upper and lower bowel disease; and the pattern of collateral circulation after coronary disease and surgical devices for improving this.

On the medical floors research is being carried on into such aspects of the cardiopulmonary system as normal and abnormal alveolar capillary gradients in the lungs; the early functional changes in chronic bronchitis; metabolic exchanges between the peripheral muscles and the myocardium under varying conditions; and intestinal absorption with particular reference to the use of the stable isotope nitrogen 15.

PREVALENCE OF RHEUMATIC DISORDERS

IN this country the prevalence of rheumatoid arthritis at any one time is 2·5% in men and 6·1% in women. This estimate was given by Dr. J. S. Lawrence, director of the Empire Rheumatism Council's field survey unit, at a press conference in London on Nov. 24. The estimate is based on a detailed four-year survey of 1700 people in an urban area and of 900 in a rural area. This survey also showed that at 65 some 97% of men and 98% of women have X-ray evidence of osteoarthritis, though in about 35% of these cases the disease causes no incapacity. The prevalence of spondylitis in the population as a whole is estimated at 0·3%; and the prevalence of gout is likewise put at 0·3%. The survey brought to light two significant findings: first, that there is a hereditary tendency in some forms of rheumatoid arthritis; and secondly that 1 person in about 20 suffers at some time from acute rheumatism or polyarthritis, resembling rheumatic fever but not affecting the heart.[1]

Dr. W. S. C. Copeman, chairman of the Council, commenting on the survey, remarked that it indicated that in Britain at any one time 5,726,000 people—that is, just over 14% of the adult population—have one of these severe forms of arthritis. Obviously, he said, we need more and better hospital facilities for treatment, more doctors trained to cope with these diseases, and more research.

H. J. McCurrich Prize

The Regional Hospitals' Consultants and Specialists Association is offering this prize (100 guineas) in 1962 for an essay on a medical or surgical topic written by "qualified hospital staff up to and including senior registrars" during tenure of office in hospitals in England and Wales. Further details may be had from the secretary of the Association, 47, Lincoln's Inn Fields, London, W.C.2.

1. See *Lancet*, Sept. 3, 1960, p. 535.

University of London

Dr. Denis Hill, senior lecturer in the department of clinical neurophysiology at the Institute of Psychiatry and lecturer in psychological medicine at King's College Hospital Medical School, has been appointed to the chair of psychiatry at Middlesex Hospital Medical School.

Dr. Hill, who is 47 years of age, was educated at Shrewsbury School and St. Thomas's Hospital. After qualifying in 1936 he held a house-appointment at Bethlem Royal Hospital and in 1938 he became chief assistant in the department of psychological medicine at St. Thomas's. During the late war he was a psychiatric specialist in the Emergency Medical Service. In 1947 he was appointed physician and lecturer in psychological medicine at King's College Hospital and in 1948 he was appointed to the staff of the Institute of Psychiatry and the Maudsley Hospital. He was elected F.R.C.P. the following year. From 1956 to 1960 he was a member of the Medical Research Council. In 1950 he edited a symposium on Electro-encephalography and he has also published papers on its applications to psychiatric problems, on medical education, and on the place of psychiatry in medicine.

Mr. Ian MacGillivray, senior lecturer in the department of midwifery in the University of Aberdeen, has been appointed to the chair of obstetrics and gynæcology at St. Mary's Hospital Medical School.

Mr. MacGillivray, who is 40 years of age, was educated at Vale of Leven Academy, Alexandria, and the University of Glasgow. He qualified in 1944 and was awarded a Gardiner research scholarship. Later he became lecturer in midwifery at the University of Glasgow and senior registrar at the Royal Maternity Hospital. In 1953 he was appointed lecturer in obstetrics and gynæcology at the University of Bristol and he took up his present appointment in 1955. He graduated M.D. in 1953 and was elected F.R.C.O.G. last year. His published work includes papers on renal, hepatic, adrenal and pituitary lesions in pregnancy and epidemiological and biochemical studies in pre-eclamptic toxæmia.

Dr. D. G. Evans, F.R.S., director of the department of biological standards at the National Institute for Medical Research, has been appointed to the chair of bacteriology and immunology at the London School of Hygiene and Tropical Medicine.

On Oct. 12 the degree of M.D. was awarded to R. S. Williams.

At recent examinations for D.P.M. the following were successful:

Joan Tugwell, H. M. N. Rees, Hilary Richards.

University of Edinburgh

Dr. G. M. Carstairs, director of the Medical Research Council Unit for Research on the Epidemiology of Psychiatric Illness, Tavistock Square, London, has been appointed to the chair of psychological medicine in succession to the late Prof. Alexander Kennedy.

Dr. Carstairs, who is 45, was born in India where his father was a Church of Scotland missionary. He was educated in Edinburgh at George Watson's College and the university, where he read arts as well as medicine and was medallist in fine art. In 1941 he graduated M.B. and after holding house-posts he served as a medical officer in the Royal Air Force in Europe and the Far East, mainly with No. 3 (Fighter) Squadron with whom he learned to fly. During the war he became interested in social anthropology, particularly in the influence of cultural environment on personality development. After the war he was senior registrar at Warneford Hospital, Oxford. During 1948–49, with a Commonwealth Fund fellowship, he studied social anthropology under Dr. Margaret Mead in New York in preparation for two years of field studies in primitive village communities in Rajputana. These researches were published in his book *The Twice Born* (1957). Before taking up his present post in 1960 Dr. Carstairs was assistant director of the M.R.C. social psychiatric research unit and an honorary consultant at the Maudsley Hospital.

Dr. D. M. Weir has been appointed lecturer in bacteriology, and Mr. J. D. O. Loudon part-time lecturer in obstetrics and gynæcology.

Royal College of Surgeons of England

The annual meeting of fellows and members is to be held on Wednesday, Dec. 7, at 3.30 P.M., at the College, Lincoln's Inn Fields, London, W.C.2.

Royal College of Obstetricians and Gynæcologists

At a meeting of the council on Nov. 26, with Mr. A. C. H. Bell, the president, in the chair, Prof. Derk Crichton (Durban, South Africa) was appointed the William Blair-Bell lecturer for 1961, and Prof. C. H. G. Macafee the William Meredith Fletcher Shaw lecturer. Mr. H. H. Francis was awarded a Bernhard Baron travelling scholarship, Dr. Bruce Eton and Dr. G. A. Humphreys Green-Armytage travelling scholarships, and Dr. J. S. Scott the Edgar-Gentilli prize.

The following were admitted to the membership:

Mavis F. Anderson, F. W. Van der Westhuizen.

The diploma in obstetrics was awarded to the following:

Robert Abendstern, E. I. Adam, Ezekiel Adewumi Bolaji Adenuga, J. B. Akingba, J. M. Allan, J. G. Allardice, A. J. R. Anderson, J. P. Andrew, D. J. Annal, Madhusudan Biharilal Atit, Sudha Madhusudan Atit, George Atkins, S. H. Aynsworth, Judith M. Babb, Clarice A. Baker, D. H. Ball, Ann D. Banister, Margaret Baron, Isabelle B. Barrie, P. C. Barrington, Anne C. Bayley, M. D. Begley, D. L. Belcher, S. M. Berger, A. T. Bevan, J. S. Bevan, J. E. Bewley, Beryl Beynon, Suniti Kumar Bhattacharyya, A. R. Bingham, Geoffrey Birchall, Anne W. Birt, Sybil Birtwistle, R. B. B. Bishton, D. H. Black, J. A. Blecher, Henry Bodsworth, H. F. Bolton, M. G. Bradley, Barrie Breeze-Stringfellow, Beatrice M. Brown, K. A. C. Brown, Judith C. H. Bullen, R. A. Bunting, L. J. Burton, Christine M. Butler, P. R. Butler, K. N. Butteriss, W. D. Callum, I. G Campbell, I. G. Carnegie-Brown, R. M. Carson, P. A. Carter, R. N. Carter, J. M. Chadwick, Vimla Chaudhry, P. J. Chaudoir, I. G. Chisholm, R. S. Churchill, R. G. Clark, Daphne C. K. Clarke, Peter Cochrane, G. F. Cockings, R. H. L. Cole, Daniel Connan, Alison R. Coutts, D. H. G. Cowie, Jane M. Craig, W. S. R. Craig, H. E. Cramp, Jane M. Critchley, Matilda E. Cuming, J. B. Davis, R. P. Davis, Anne A. N. Day, W. R. Dean, Harvey Dexter, P. N. Dixon, Jeane B. Donaldson, J. A. Driscoll, J. R. E. Edmondson-Jones, A. J. Ellison, A. J. H. Ellison, David Emerson, William Erskine, Iain Esslemont, Beryl H. Evans, G. R. L. Evans, J. F. Farrall, C. J. Farrer, M. J. Feitelberg, Jean M. Fell, P. L. Ferguson, M. A. Ferri, J. A. C. Fisher, P. G. T. Ford, D. F. Foster, William Foster, Patricia A. J. Freeman, R. F. R. Gardner, I. I. Gaston, E. E. Genever, D. M. George, E. R. Gibbons, Phyllis M. Gibbons, Janet I. Gibson, Sidney Ginsberg, P. J. Gladders, Selwyn Glick, J. B. Gnanapragasam, Alan Gooding, G. T. Gooding, R. A. Gould, T. R. Gould, G. S. Graham, Colette C. Green, Ronald Greenbaum, P. R. Greenfield, R. A. W. Guthrie, Judith M. Hall, M. J. Hall, S. W. D. Hall, T. J. Hall, A. W. Harris, D. F. Harrison, A. S. Hartt, Mehar Qamrul Hasan, Gerald Hass, D. A. Hastings, J. P. Hawe, M. J. Hegarty, R. S. Hickling, J. H. Higgins, F. R. Hilborne, D. G. W. Hollands, J. R. Holliday, P. S. Hollingworth, J. G. Holmes-Smith, Marie K. Housley, E. G. Hoyen-Chung, V. P. Hynes, Michael Ibberson, G. D. Ikedife, E. A. Ikomi, D. H. Irvine, Alberta E. Irwin, Teresiamura Jacob, P. W. James, I. W. Jamieson, Sadrudin Alibhai Janmohamed, D. C. Jeffery, D. M. Jenkins, D. L. Jennings, W. A. Johns, J. K. Johnson, M. L. Johnson, P. A. Johnson, I. N. L. Johnston, A. J. Jordan, John Keane, Denis Keating, Trixie Kelly, Martin Kelvin, N. B. Kirkland, Saramma Koshy, Serge Kunstler, F. K. A. Laing, W. I. Lamont, Marjorie M. Langmuir, Osafo Lartey, C. J. N. Lawson, D. J. Lawson, P. M. Leary, J. A. S. Lees, M. M. Lees, J. E. Leng, P. M. Lenten, R. B. Levy, D. W. Lewis, H. M. Liegeois, J. P. Lissenden, J. R. B. Livingstone, J. K. Lloyd, J. O. Lloyd-Jones, V. J. E. D. Lobo, Barbara A. Lockley, R. M. Lodge, K. E. Luckman, M. V. McCabe, T. N. McCarthy, B. W. M. Macartney, Jean L. McColl, G. C. A. MacDevitt, J. D. Macdonald, R. C. Macfarlane, J. P. MacFaul, R. F. McGann, J. C. McGrand, Helen R. McKilligin, J. G. McLaggan, W. S. S. Maclay, Hugh Macmaster, D. C. McNeill, Stephen McPherson, R. L. McRitchie, P. D. Maddocks, B. W. Maitland, Valerie Major, Debabrata Mallik, J. W. Maltby, Annamma Mammen, William Manton, J. A. Mathews, R. D. Mathias, Hazel J. Matthews, Thomas Mawdsley, R. E. May, Hamida Sultana Memon, Romola A. Menezes, G. M. Milne, R. G. Milne, Alison M. Molyneaux, M. W. Moncrieff, P. R. Monk, K. A. M. Moore, M. J. Moore, G. L. Morgan, J. F. Morris, K. A. A. Mourin, E. S. Mucklow, I. S. Muir, Subimal Mukerjee, H. D. R. Munro, Helen M. G. Murray, Mya Mya, E. A. Neville, Margaret P. Newton, J. D. Nicholas, J. B. Nichols, Jennifer M. Nixon, J. B. Nuttall, P. P. S. Nylander, F. A. Olapade, Zubeda Osman, Alexander Osmond, J. D. Owen, Glenys R. Packer, M. J. Page, D. J. Palmer, Indu Fakirbhai Patel, A. W. Patterson, K. R. Peel, M. G. Peters, J. A. Phelan, F. S Plumpton, Margaret D. Power, Audrey J. N. Price, H. V. Price, J. D. Price, J. L. Price, D. J. Prosser, H. S. Radden, Tadeusz Radomski, P. G. Rae, P. B. Read, B. L. E. C. Reedy, Shirley J. Richards, Margaret Richardson, A. E. Ridley, R. M. Ridsdill-Smith, J. A. Rigby, Catherine O. L. Rimington, J. K. Roberts, Irene J. Robertson, Moira C. Robertson, R. W. K. Rogers, J. N. Roskilly, K. W. Rowden, W. N. T. Roy, Elizabeth M. Russell, J. L. Russell, J. G. Russell, Lorna J. Rust, Naomi J. Sage, S. S. Sanders, I. W. H. Scott, M. D. Scott, A. H. Sears, M. S. Seltzer, C. R. Sexton, Jean Shackleton, H. J. Shapiro, E. A. Shaw, F. D. Skerrett, J. O. Sibthorpe, R. I. D. Simpson, R. O. Skinner, E. C. Smart, Frederick Smith, R. C. Smith, J. K. Snell, Christine A. Snodgrass, J. B. Sorapure, D. F. Spencer, G. M. Steiner, W. J. Stephen, B. J. Stevenson, W. B. Stewart, Sheila M. Strachan, Mylvaganam Sundaralingam, H. W. Sutherland, G. H. Swapp, R. M. R. Taylor, R. W. Taylor, William Taylor, Henry Teed, I. P. Thew, P. S. Thomas, Andrew Thomson, Freda M. Tomlinson, Elisabeth A. Tooth, John Tudor, Lorna S. Vethavanam, J. C. Voigt, Ruth E. H. Wainwright, Pamela Walton, J. T. Ward, Joyce Warner, M. S. Warwick, P. H. Waterfield, R. R. Watkin, R. A. Watkins, A. J. Watson, A. B. Watson, Dorothy A. Watson, Anne H. White, James Wightman, Anne M. Wigley, Aled Williams, G. L. Williams, Barbara J. Willmer, Derek Wilson, J. M. Wilson, Marie B. Wilson, C. E. R. Winer, G. B. Wolloff, J. M. Woodhead, Michael Woodliff, R. G. Wrangham, Maureen L. Wyllie, H. N. Young.

Treacher Collins Prize

The subject chosen for the next award of this essay prize (£100) which is offered triennially by the Ophthalmological Society of the United Kingdom, is demyelination and the eye. The closing date for submitting essays is Dec. 31, 1962. Further particulars may be had from the hon. secretary of the society, 47, Lincoln's Inn Fields, London, W.C.2.

British Medical Association

On Thursday, Dec. 15, at 5.30 P.M., at B.M.A. House, Tavistock Square, London, W.C.1, Mr. Henry Osmond-Clarke will open a lecture-discussion on fractures around the wrist.

British Association of Physical Medicine

A meeting of this Association will be held on Friday, April 21, at the Royal National Orthopædic Hospital, Stanmore, and on Saturday, April 22, at Westminster Hospital, London, S.W.1.

Royal Society of Edinburgh

David Anderson-Berry Medal and prize (£100).—An award will be made in 1961 for recent work on the effects of X rays and other forms of radiation on living tissues. Applications for the prize, or proposals on behalf of others, must be in the hands of the general secretary of the society, 22, George Street, Edinburgh, 2, Scotland, not later than March 31.

Living Conditions, Health, and Economic Development

The International Medical Association for the Study of Living Conditions and Health will hold a conference on this subject from Sept. 29 to Oct. 1 at St. Vincent, Aosta Valley near Turin, Italy. Further particulars may be had from the general secretary of the Association, Burggasse 71/I/6, Vienna 7, Austria.

Central Council for Health Education

The annual conference of this Council will be held on Thursday, Jan. 26, at 10.30 A.M., at the National Film Theatre, London, S.E.1. The theme of the conference will be the Road to Maturity and the speakers will include Dr. David Stafford-Clark and Dr. M. S. Harvey. Further particulars may be had from the medical director of the Council, Tavistock House North, London, W.C.1.

International Congress of Neurology

This congress will be held from Sept. 10 to 15 in Rome. Subjects to be included in the programme are neurological disorders in porphyria, phenylketonuria, and galactosuria; brain disturbances associated with cardiopulmonary disorders; and aphasia. On Sunday, Sept. 10, a symposium of neurological genetics will be held in conjunction with the international conference of genetics. Further particulars may be had from Dr. G. Alemà, Viale dell'Università, 30, Rome.

Sir Robert Platt, P.R.C.P., has been elected to the honorary fellowship of the American College of Physicians. This will be conferred on him in May when he visits the United States to give the Lilly lecture.

Dr. G. W. Corner, FOR.MEM.R.S., historian of the Rockefeller Institute, New York, and director emeritus, department of embryology of the Carnegie Institution of Washington, has been appointed executive officer of the American Philosophical Society, Philadelphia. He will retain a connection with the Rockefeller Institute as visiting professor.

On Monday, Dec. 5, at 8.15 P.M., at the Marlborough Day Hospital, 38, Marlborough Place, London, N.W.8, Dr. Joshua Bierer will speak on the Future of the Mental Health Services in Great Britain.

A meeting of the Biochemical Society will be held on Friday, Dec. 16, at 10.10 A.M., at Guy's Hospital Medical School, London, S.E.1.

A meeting of the medical and scientific section of the British Diabetic Association will be held at University College Hospital, London, W.C.1, on Friday and Saturday, April 7 and 8.

Appointments

CLARK, E. M., M.R.C.S., D.M.T. & H.: assistant M.O.H., Nottingham.
DALLACHY, RUSSELL, M.B. Glasg.: consultant pathologist, West Cumberland group of hospitals.
MEEHAN, MARY T., M.B. N.U.I.: school M.O., North Riding of Yorkshire.

Middlesex County Council:

KLASSNIK, B., M.B.: assistant M.O., Tottenham and Hornsey.
NICHOLLS, JOAN H., M.B. Lond.: assistant M.O., Tottenham and Hornsey.
SETHI, G. S., M.B. Punjab, D.T.M. & H., D.P.H.: assistant M.O., Tottenham and Hornsey.